Astellas Pharma
Isavuconazole

Food and Drug Administration

Anti-Infective Drug Advisory Committee

January 22, 2015

Compound Overview and Clinical Pharmacology

Bernhardt Zeiher, MD, FACP, FCCP

Executive Vice President

Global Development

Astellas Pharma

Agenda

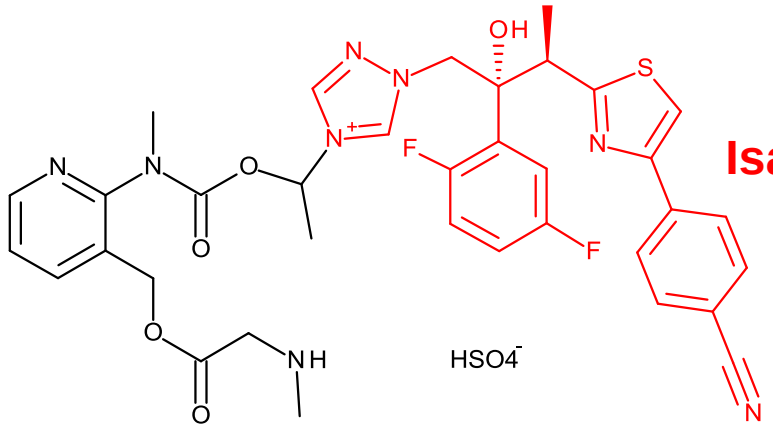
Compound Overview **Clinical Pharmacology**	**Bernhardt Zeiher, MD, FACP, FCCP** Executive Vice President Global Development
Disease Background **Unmet Need**	**Andrew Ullmann, MD, FIDSA** Professor of Infectious Diseases University of Wurzburg, Germany
Efficacy	**Rochelle Maher, MS** Senior Director Global Development Project Leader
Safety	**Salim Mujais, MD** Vice President Global Medical Head Infectious Disease
Benefit-Risk	**Bernhardt Zeiher, MD, FACP, FCCP**

Attending Experts

David Andes, MD	Professor of Infectious Disease University of Wisconsin
Oliver Cornely, MD	Professor of Translational Research University Hospital of Cologne
Ashraf Ibrahim, PhD	Professor of Medicine University of California, Los Angeles
Achim Kaufhold, MD	Chief Medical Officer Basilea Pharmaceutica Ltd.
Peter Kowey, MD	Professor of Medicine and Clinical Pharmacology Chief, Division of Cardiovascular Disease Lankenau Hospital and the Main Line Health System

Isavuconazonium: Novel Prodrug

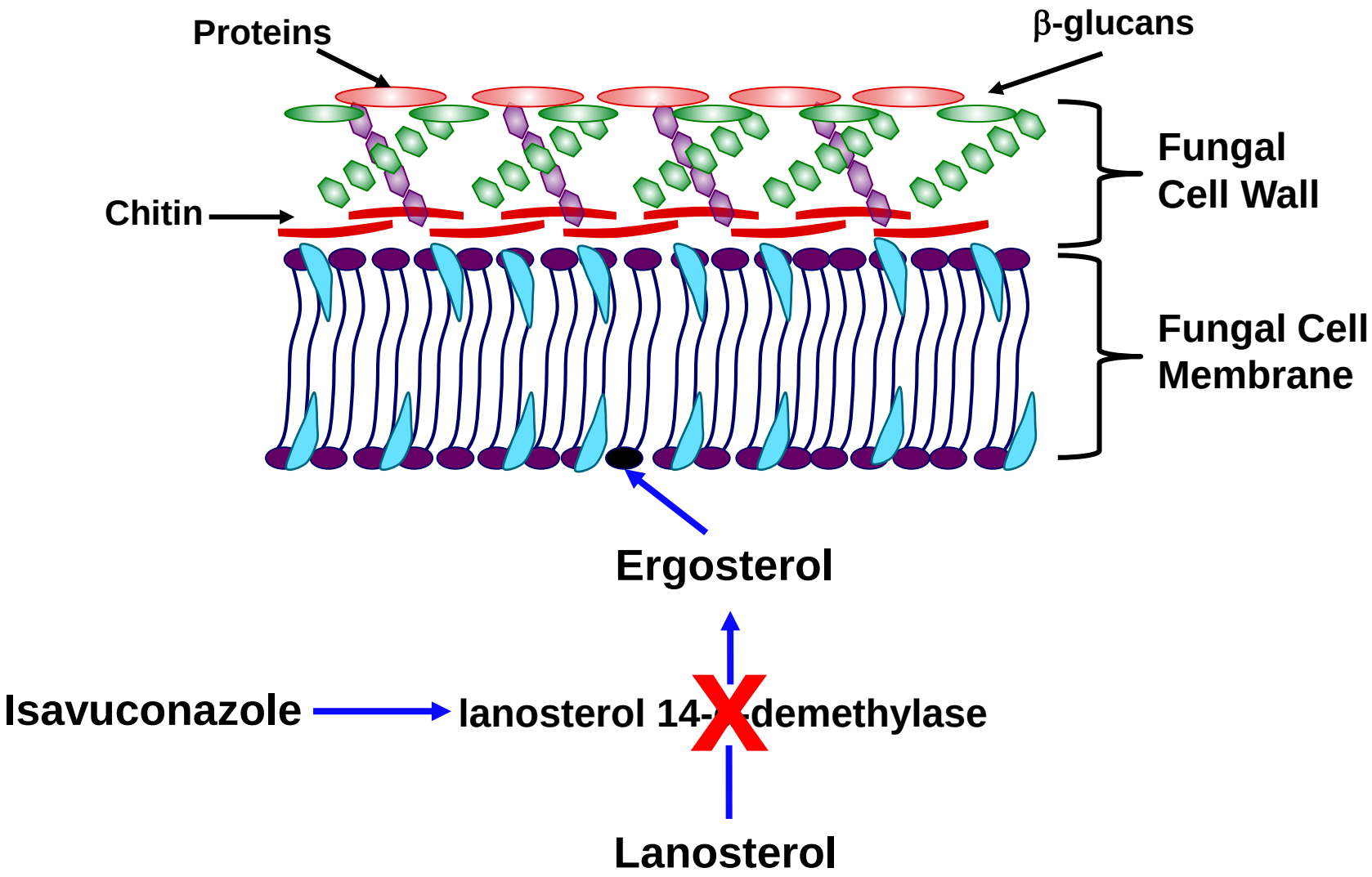
Cleavage Product



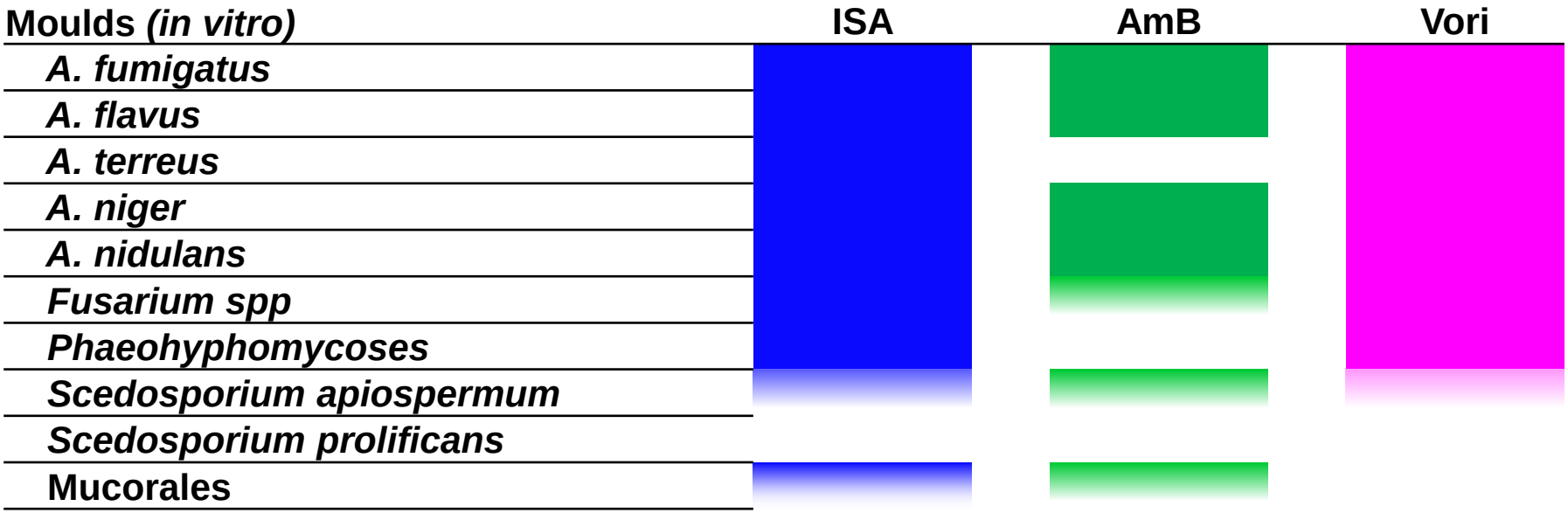
Isavuconazole (ISA)

- IV and oral formulations
- Rapidly hydrolyzed by esterases
- Active moiety isavuconazole
- Highly water soluble prodrug
  - IV formulation: no cyclodextrin

Isavuconazole Mechanism of Action



Isavuconazole: Broad Spectrum of Activity

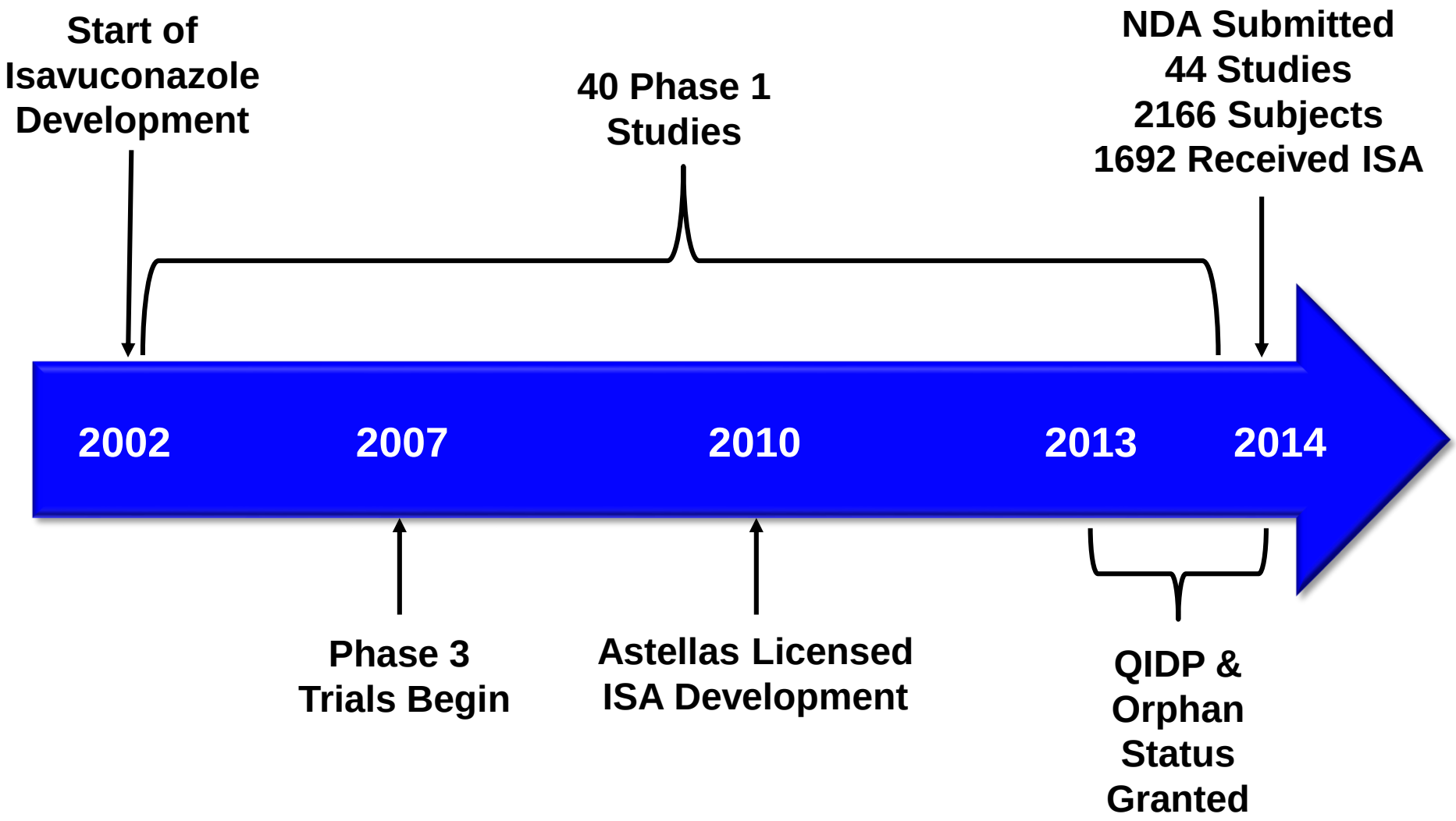


In vivo reduction in fungal tissue burden and increase in survival

- Disseminated and pulmonary aspergillosis
  - AUC / MIC correlated with outcome
- Pulmonary mucormycosis

AmB = amphotericin B; Vori = voriconazole

Isavuconazole Development Program



Proposed Indication

- Isavuconazonium is indicated for patients 18 years of age and older in the treatment of
  - Invasive aspergillosis
  - Invasive mucormycosis

Clinical Pharmacology

Well-Characterized Clinical Pharmacology

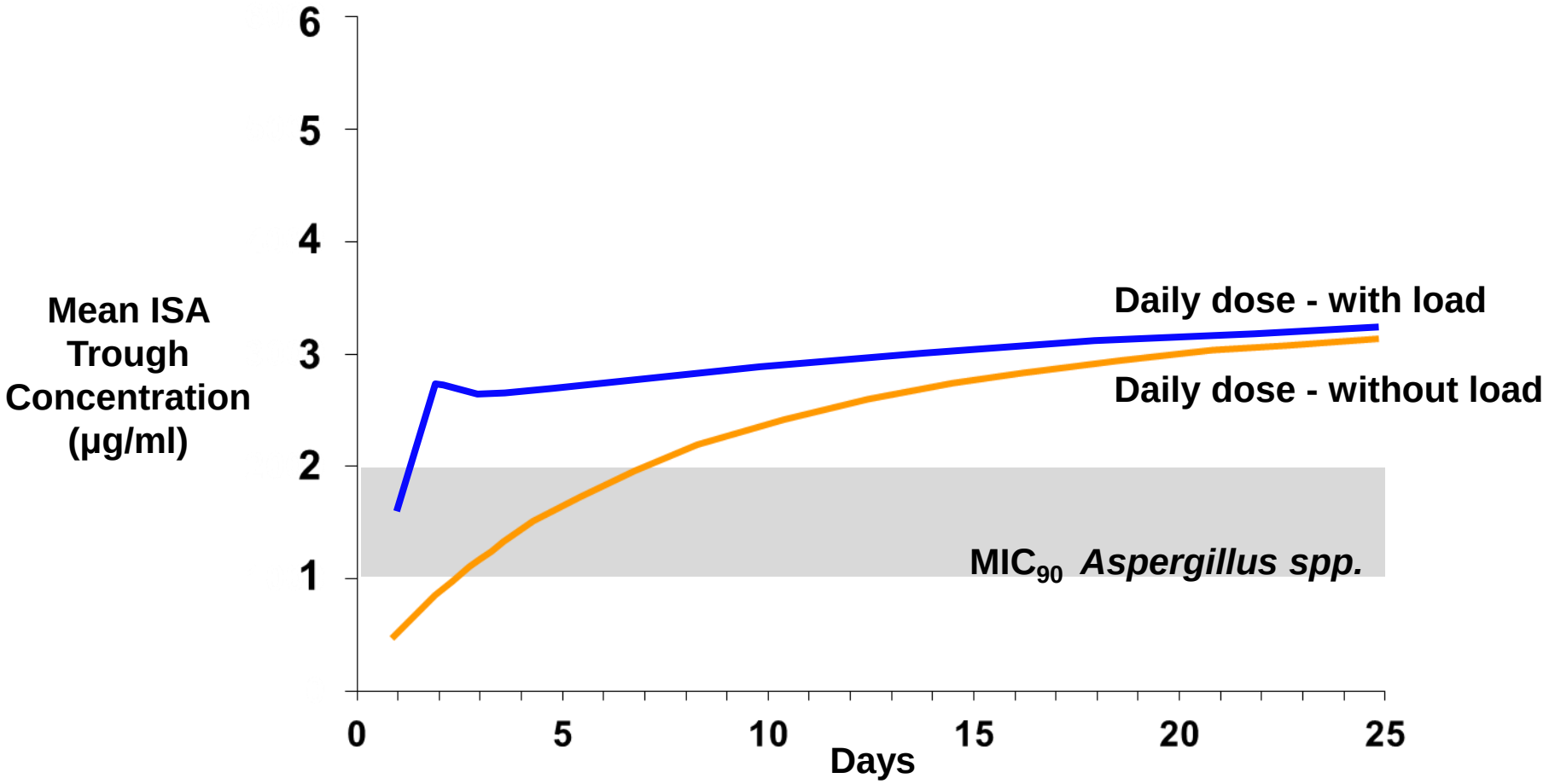
- 40 clinical pharmacology studies
  - Dose proportional increases in exposure
  - Rapidly absorbed with 98% oral bioavailability
  - No pH or food effect
  - Large volume of distribution (450L)
  - CYP3A4 metabolism
  - <1% of unchanged drug excreted by kidneys
  - Long terminal elimination half-life (~130 hours)
  - No dose adjustment required in elderly, hepatic or renal impairment

Drug-Drug Interaction Potential

CYP	Substrate	Isavuconazole	Voriconazole
3A4	Midazolam	↑ 2.0 fold	↑ 10.3 fold
	Sirolimus	↑ 1.8 fold	↑ 11.0 fold
1A2	Caffeine	NCS	NCS
2C8	Repaglinide	NCS	NCS
2C9	Warfarin	NCS	↑ 2.0 fold (PT)
2C19	Omeprazole	NCS	↑ 4.0 fold
2B6	Bupropion	↓42%	↑ 1.3-fold
2D6	Dextromethorphan	NCS	NCS

NCS: no clinically significant change; PT: prothrombin time

Isavuconazole: Rapid Achievement of Steady State Requires Loading Dose



- 200 mg IV or orally administered every 8 hours for a total of 6 doses
- Followed by a 200 mg once daily IV or oral dose

Disease Background and Unmet Medical Need

Andrew J. Ullmann, MD, FIDSA
Professor of Infectious Diseases
University of Wurzburg, Germany

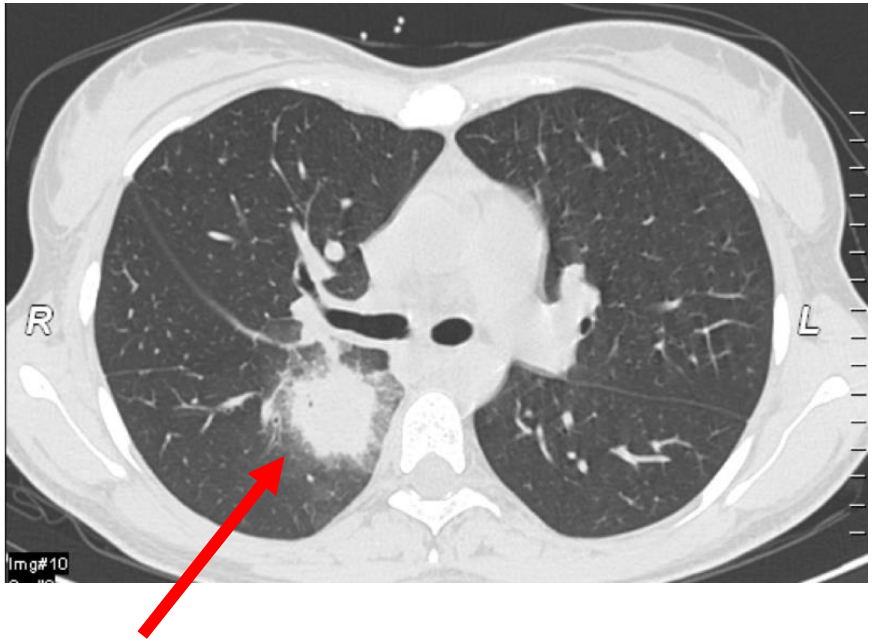
Invasive Fungal Infections: Key Points

- Typically occur in severely immunocompromised patients
  - High comorbidities
- Rare infections
  - ~12,000 / year aspergillosis in US[1,2]
  - ~500 / year mucormycosis in US[3]
- Difficult to diagnose and treat
  - High morbidity and mortality
  - Limited therapeutic options

1. Tong et al., 2009. 2. Warnock, 2007. 3. Rees et al., 1998.

Clinical Presentation: Invasive Aspergillosis

- Non-specific clinical symptoms
  - Fever
  - Cough
  - Sputum
  - Pleuritic pain
  - Hemoptysis
  - Dyspnea



Difficulty in Diagnosis of Aspergillosis

- Possible disease[1]
  - Host factors and radiology
- Proven and probable disease[1]
  - Mycologic criteria
    - Cultures
    - Histology
    - Serum or bronchoalveolar lavage (BAL) galactomannan
- Treat with mould-active antifungal unless alternative etiology identified

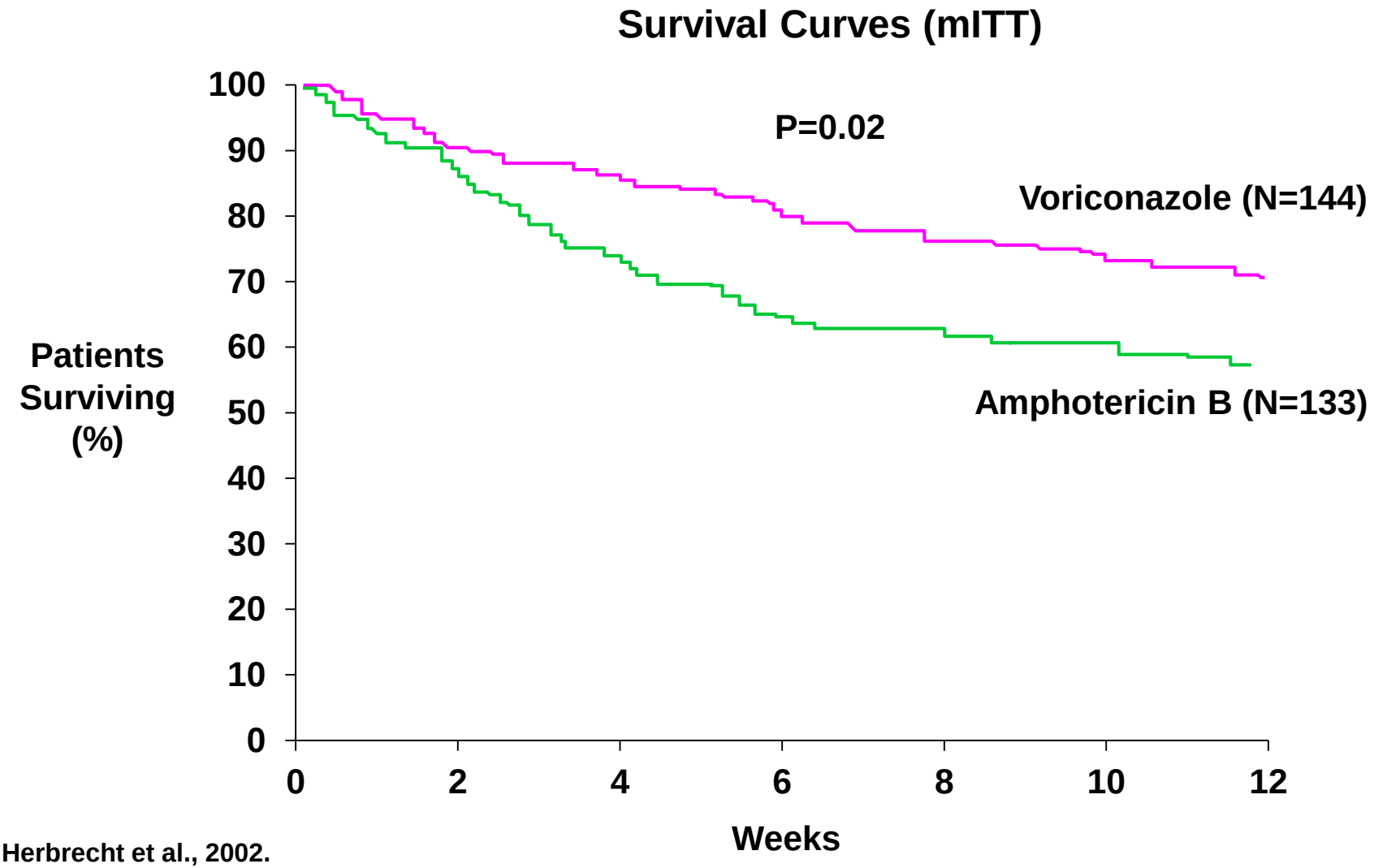
1. De Pauw et al., 2008.

Essential to Treat Patients with Possible Disease

- Report of autopsy data from 1,017 patients with hematologic malignancies[1]
  - 31% found to have IFD at autopsy
    - 75% not diagnosed prior to death
- Autopsy of 38 allogeneic stem cell patients[2]
  - 10 died with IFD
    - 6 deep mycoses were missed

1. Chamilos et al., 2006. 2.Sinko et al., 2008.

Voriconazole: Standard of Care in Invasive Aspergillosis



Herbrecht et al., 2002.

Voriconazole: Pharmacologic Characteristics

- Excellent activity against *Aspergillus spp.*
  - No activity vs. mucorales
- IV and oral formulations
  - IV formulation requires cyclodextrin
- Pharmacokinetic characteristics
  - Non-linear PK
  - Genetic variability in metabolism (CYP2C19)
  - Food effect
  - Potential drug-drug interactions

US prescribing Information Voriconazole, April 2014.

Voriconazole: Limitations

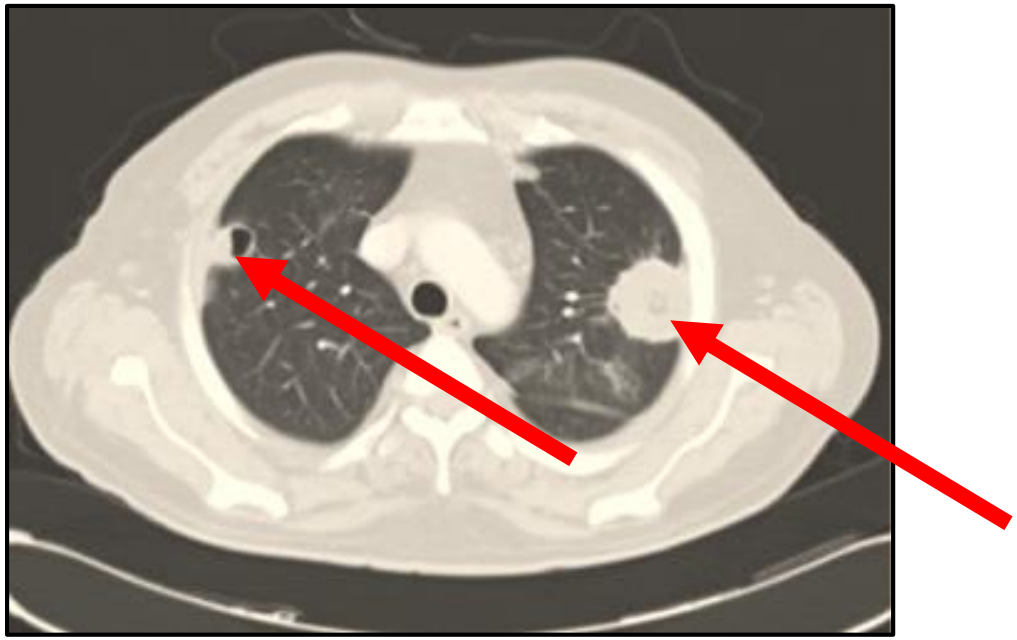
- Treatment limiting safety risks
  - Hepatic toxicity
  - Dermatological reactions
  - QT prolongation
- Safety risk specific to voriconazole
  - Visual disturbances

US prescribing Information Voriconazole, April 2014.

Current Standard of Care: Invasive Mucormycosis

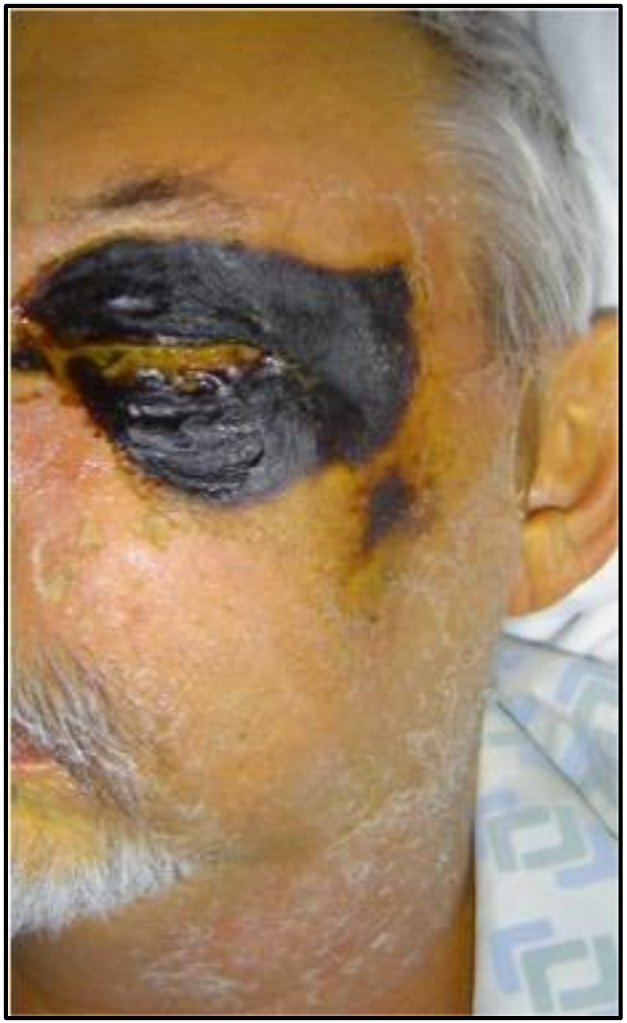
Difficulty in Diagnosis of Mucormycosis

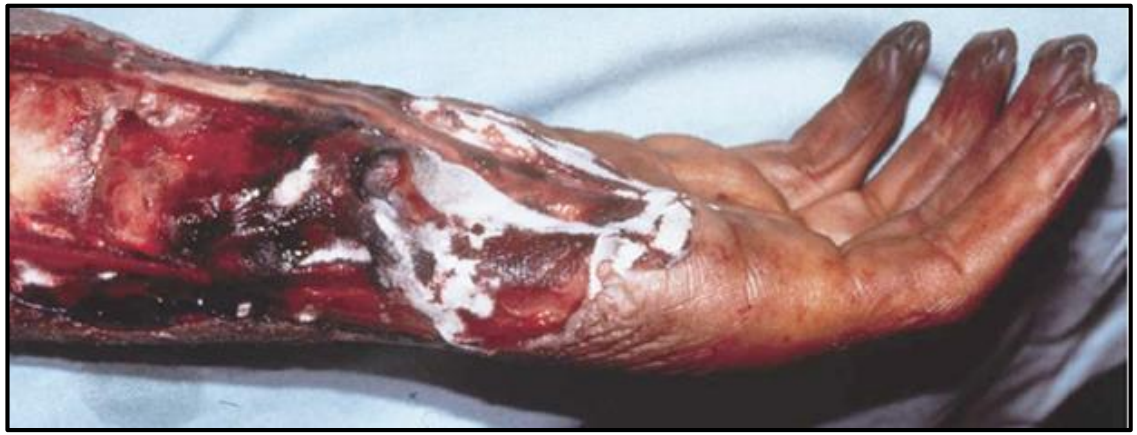
- Diagnostic criteria similar to those of aspergillosis
  - No serologic biomarker for mucormycosis
  - Relies on invasive procedures



Clinical Presentation of Invasive Mucormycosis

- Nasal and sinus disease more common than with aspergillosis
  - May invade orbit or brain
  - Requires extensive surgical debridement





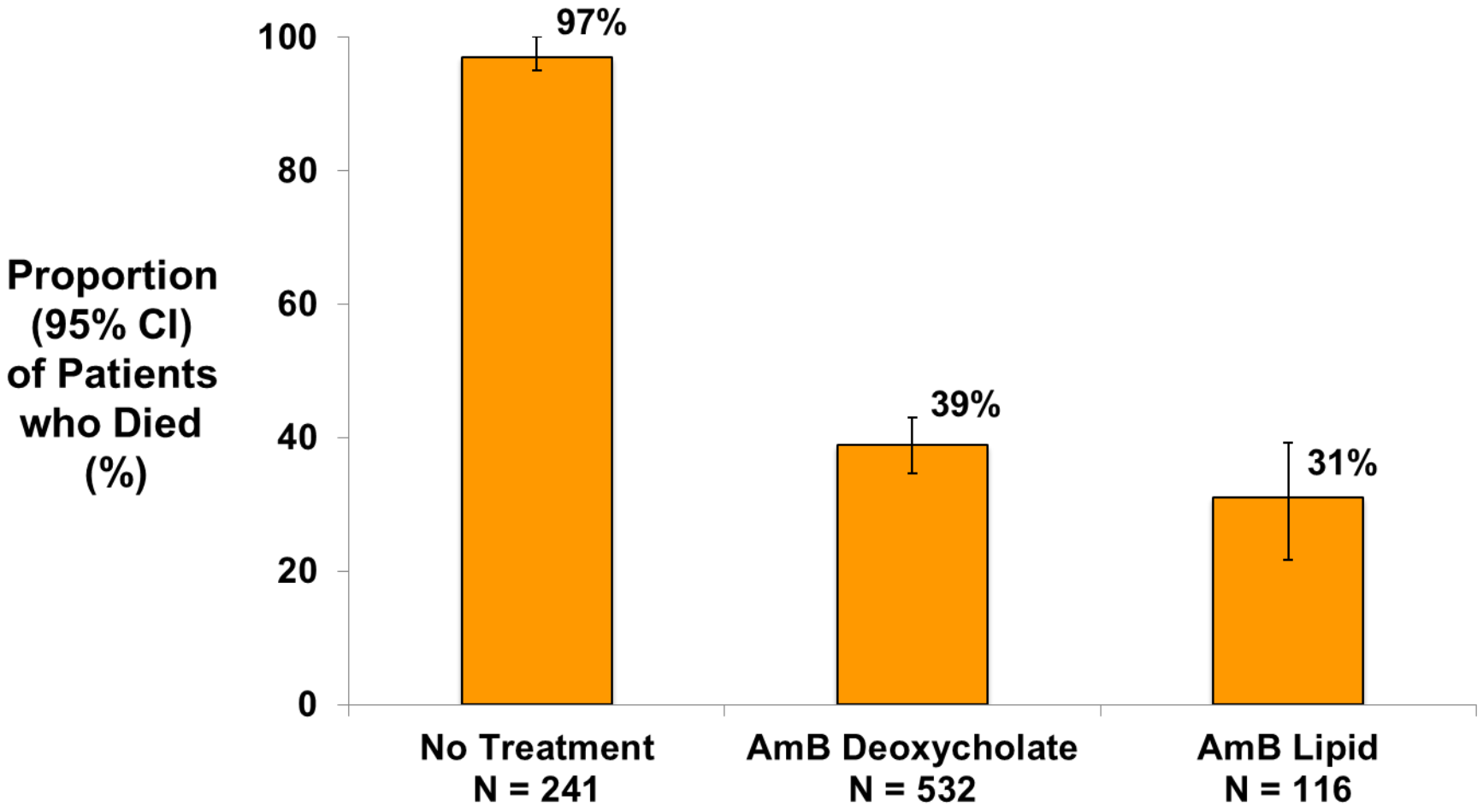
Lidor and Nunley, 1997.

Mucormycosis Treatment: Amphotericin B

- Amphotericin B Deoxycholate
  - Infusion reactions
  - Renal toxicity
    - Associated with prolonged stay in hospital and mortality[1,2]
  - Only FDA-approved therapy for mucormycosis
- Lipid formulations
  - Reduce toxicities
  - Recommended as first line therapy in EU[3]

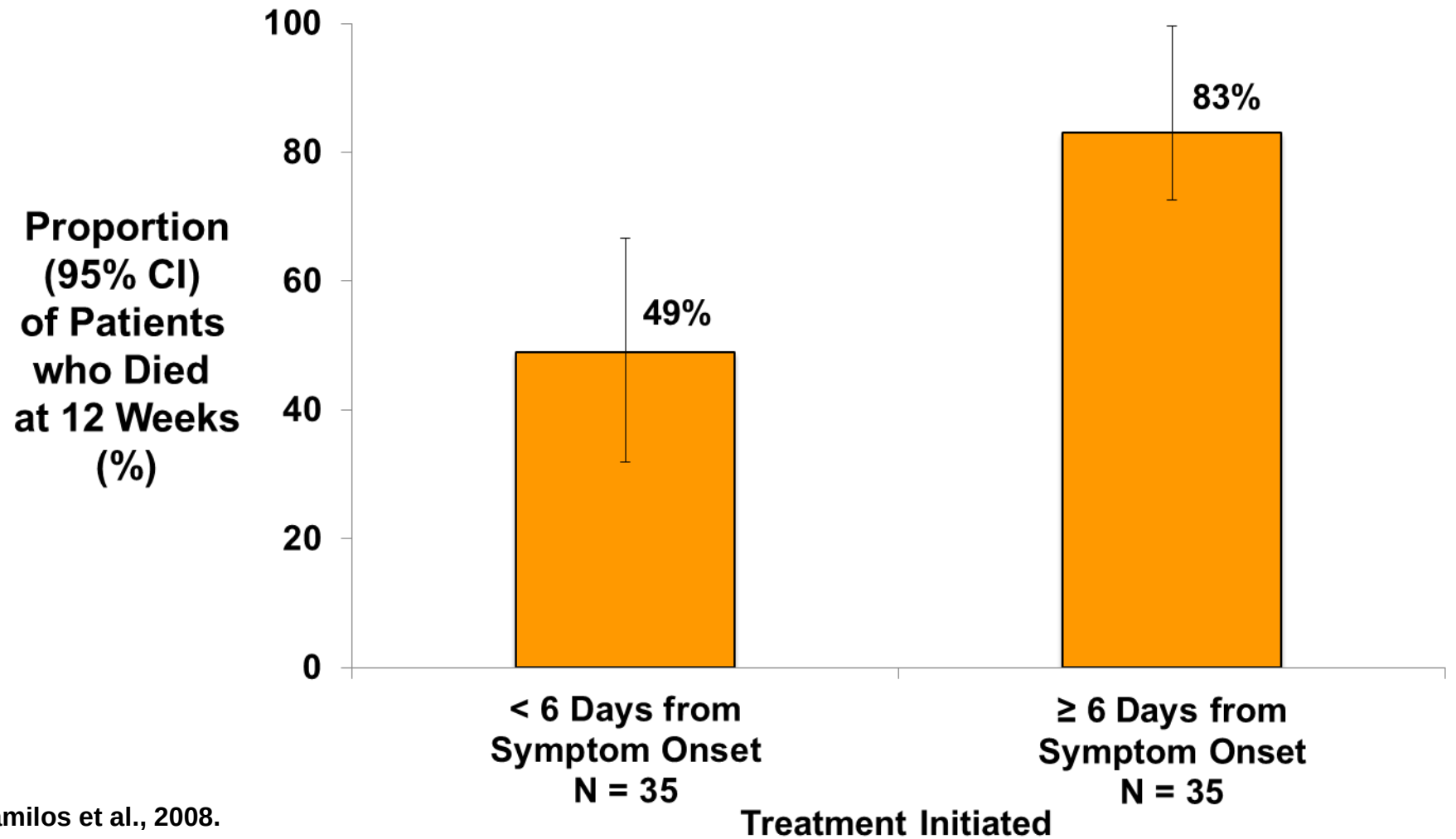
1. Bates et al., 2001; 2. Ullmann et al., 2006.; 3. Cornely et al., 2014.

Mortality Associated with Invasive Mucormycosis



Roden et al., 2005.

Impact of Delayed Initiation of Mucorales Active Antifungal Therapy



Chamilos et al., 2008.

Diagnostic Procedures and Mortality Remain Challenging

- Unsatisfactory diagnostic procedures
  - CT scanning cannot reliably differentiate between diseases
  - No reliable biomarkers
  - Culture or cytology frequently false negative
- Only two drugs approved for primary treatment of filamentous fungi

Unmet Medical Need for Additional Therapeutic Options

- High mortality
- Voriconazole
  - PK and safety limitations
  - No activity against mucorales
- Amphotericin B deoxycholate
  - Only approved option for mucormycosis
  - Significant toxicity profile

Phase 3 Study Design and Efficacy Results

Rochelle Maher, MS

Senior Director

Global Development Project Lead

Astellas Pharma

Phase 3 Program Overview

- Study 0104
  - Primary support for treatment of Invasive Aspergillosis
- Study 0103
  - Primary support for treatment of Invasive Mucormycosis

Study 0104
Invasive Aspergillosis Indication

Aspergillus Species

Other Filamentous Fungi

Study 0104: Design

- Proven / Probable / Possible invasive fungal disease (IFD)
  - All with host factors and radiologic evidence of IFD
  - Proven / Probable met protocol mycologic criteria
- International, double-blind, randomized controlled study
  - Isavuconazole compared to voriconazole
  - Treatment duration up to 84 days
- Stratification variables
  - Hematopoietic stem cell transplant (HSCT), active malignancy, geographic region
- Non-inferiority design

Study 0104: Primary Endpoint

- All-cause mortality (ACM) through Day 42
  - Pre-specified non-inferiority margin: 10%
  - Assumed ACM: 20%[1]
  - Power: 80%
  - One-sided 2.5% significance level
  - Sample size: N = 510

1. Herbrecht et al., 2002.

Study 0104: Key Secondary Endpoint - Overall Response

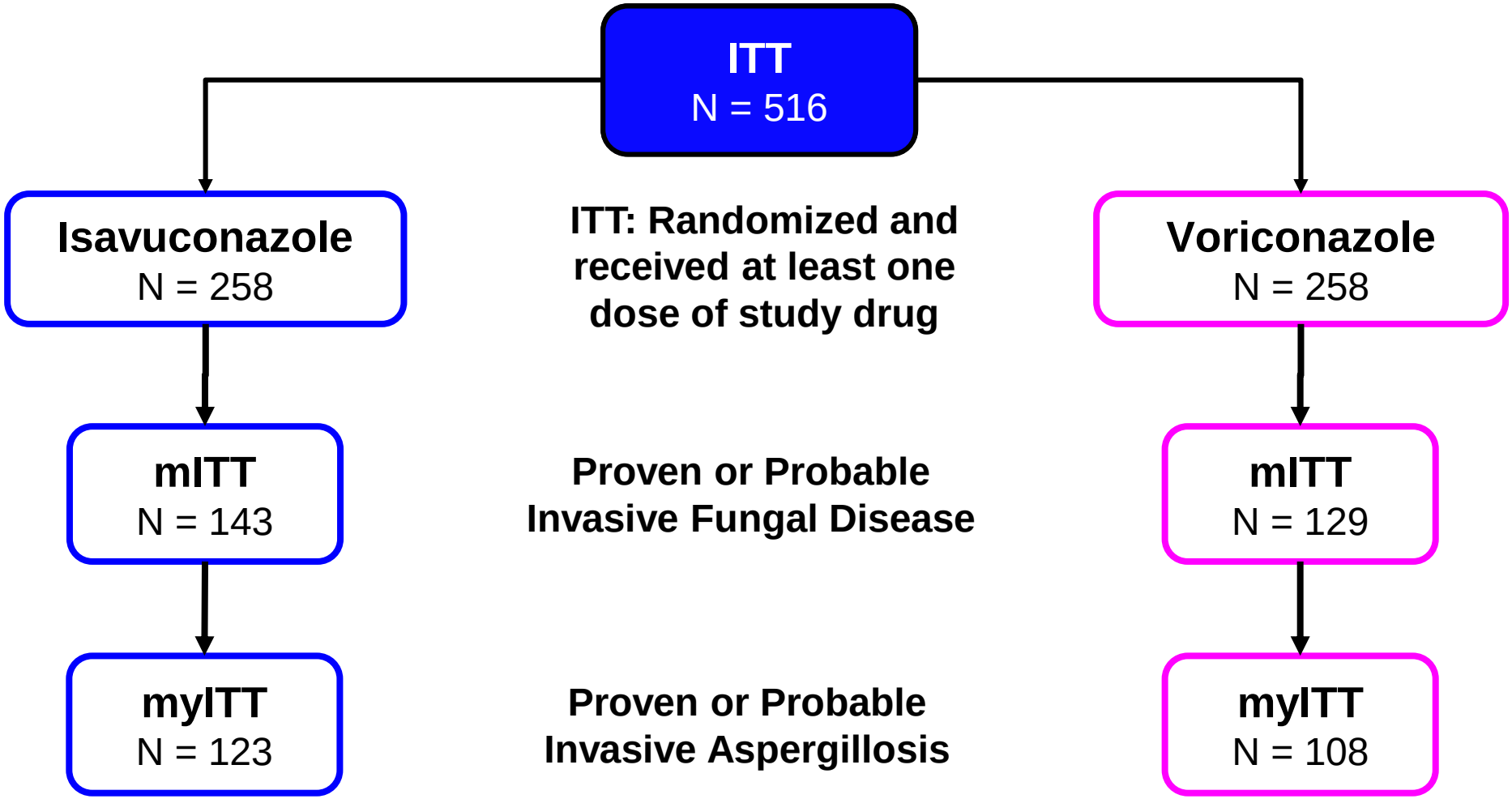
- Success defined as complete or partial overall response rate at EOT
  - Response based on clinical, radiologic, and mycologic factors
- Determined by independent, blinded, data review committee (DRC)
  - Based on EORTC / MSG criteria*[1]

***Based on criteria from European Organization for Research and Treatment of Cancer (EORTC) and Infectious Diseases Mycoses Study Group (MSG)**

1. Segal et al., 2008.

Phase 3 Study 0104: Disposition and Baseline Characteristics

Study 0104: Aspergillosis Analysis Populations



Study 0104: Mycologic Criteria (mITT)

Pathogen	Isavuconazole N = 143		Voriconazole N = 129	
	n	%	n	%
Aspergillus Species Only	49	34.3	39	30.2
Aspergillus fumigatus	32	22.4	21	16.3
Aspergillus flavus	10	7.0	12	9.3
Aspergillus terreus	4	2.8	2	1.6
Aspergillus niger	6	4.2	2	1.6
Aspergillus other	2	1.4	4	3.1
Aspergillus Plus Other Mould	3	2.1	1	0.8
Non-*Aspergillus* Species Only	5	3.5	6	4.7
Mould Species Not Otherwise Specified	14	9.8	15	11.6
Serum Galactomannan Positive Only*	72	50.3	68	52.7

*Protocol Specified Mycologic Serum GM Criteria: ≥ 0.5 x 2 or ≥ 0.7 x 1

Study 0104: Demographics

ITT Population Parameter	Isavuconazole N = 258	Voriconazole N = 258
Age (years)		
Mean (SD)	51.1 (16.2)	51.2 (15.9)
Gender, %		
Male	56.2	63.2
Race, %		
White	81.8	74.3
Asian	17.4	24.9
Black	0.4	0.4

Study 0104: Baseline Conditions

ITT Population	Isavuconazole N = 258 %	Voriconazole N = 258 %
Hematologic Malignancy	81.8	86.0
Active Malignancy	67.1	72.5
Neutropenia*	63.2	67.8
T-cell Immunosuppressant	43.0	42.2
HSCT**	20.9	19.8
Use of Corticosteroids	18.6	15.1

*Absolute neutrophil count <0.5 x 10^9/L (<500/mm^3)
**HSCT: Hematopoietic Stem Cell Transplant

Study 0104: 3rd Stratification Variable – Geographic Region

ITT Population Stratification Variable	Isavuconazole N = 258 %	Voriconazole N = 258 %
Geographic Region		
North America	11.6	10.9
Western Europe, Australia and New Zealand	40.7	41.5
Other	47.7	47.7

Study 0104: Treatment Duration

ITT Population	Isavuconazole N = 258	Voriconazole N = 258
Total Duration (days)		
Mean (SD)	47.0 (32.4)	46.4 (32.1)
Duration of IV Dosing (days)		
Mean (SD)	8.1 (8.5)	8.9 (9.6)

Phase 3 Study 0104: Efficacy Results

Study 0104: Primary Endpoint Met – All-Cause Mortality Through Day 42

ITT Population	Isavuconazole N = 258 %	Voriconazole N = 258 %
All-Cause Mortality*	18.6	20.2
Adjusted Treatment Difference (95% CI)**	-1.0 (-7.8, 5.7)	

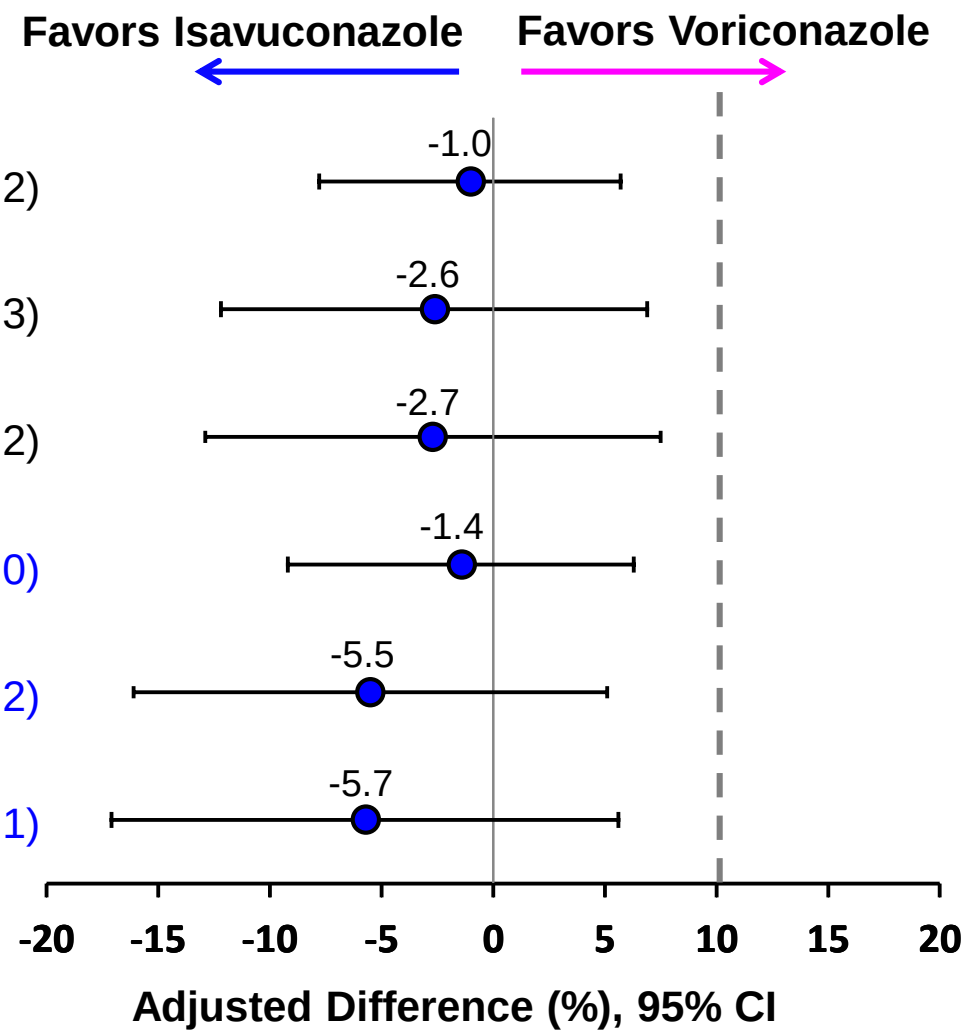
- Upper bound of 95% CI < 10% NIM

* Five (3 isavuconazole, 2 voriconazole) patients with unknown survival status were counted as deaths

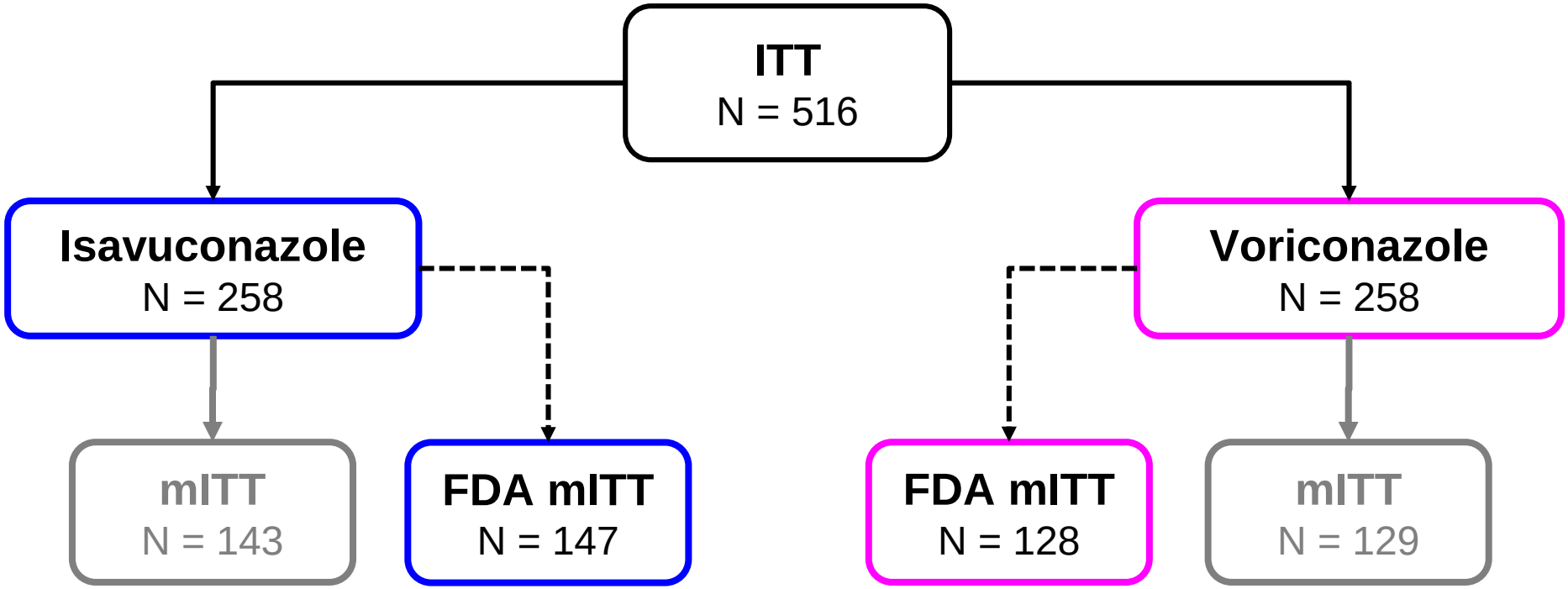
** Treatment difference (isavuconazole–voriconazole); calculated by a stratified Cochran–Mantel–Haenszel method (strata: allogeneic HSCT, active malignancy status, and geographic region)

Study 0104: Consistent Efficacy Across Analysis Populations

	Crude Mortality n/N (%) ISA	VRC
Day 42 ITT	48/258 (18.6)	52/258 (20.2)
Day 42 mITT	28/143 (19.6)	30/129 (23.3)
Day 42 myITT	23/123 (18.7)	24/108 (22.2)
Day 84 ITT	75/258 (29.1)	80/258 (31.0)
Day 84 mITT	43/143 (30.1)	48/129 (37.2)
Day 84 myITT	35/123 (28.5)	39/108 (36.1)



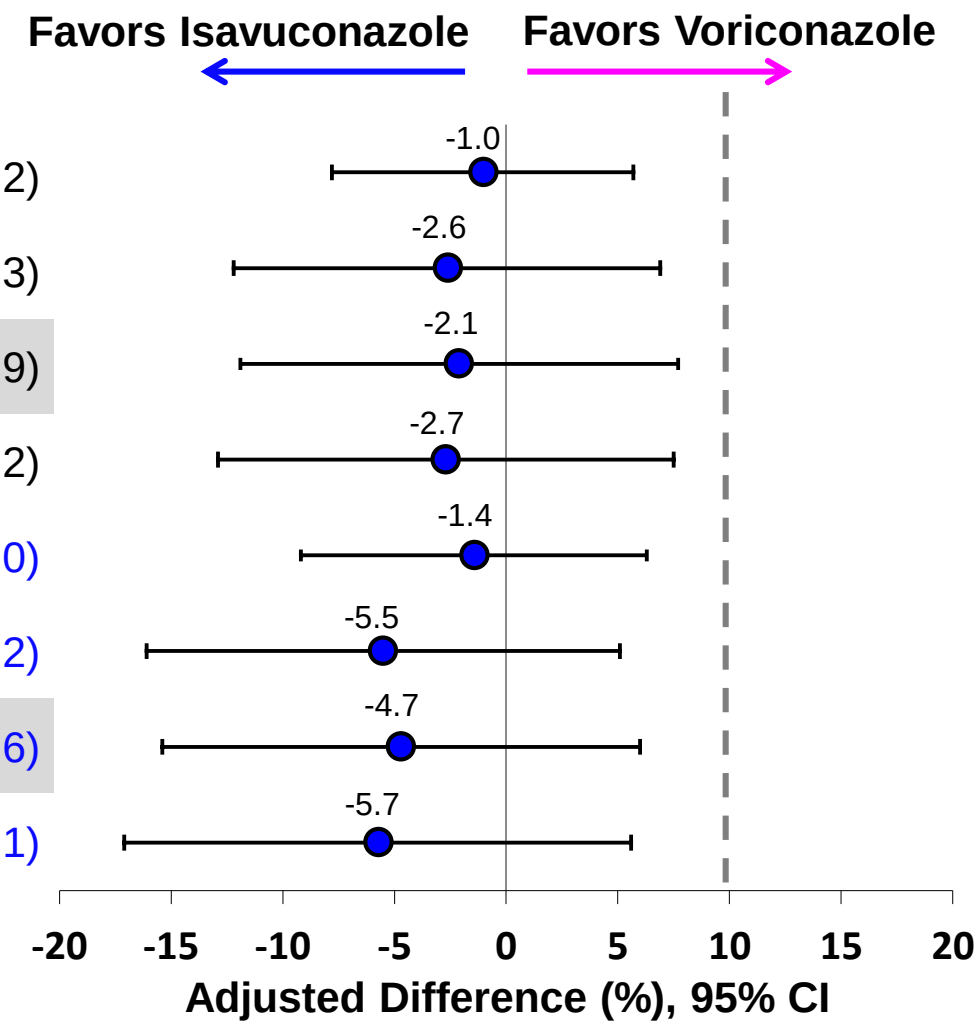
Study 0104: FDA-mITT Analysis Population



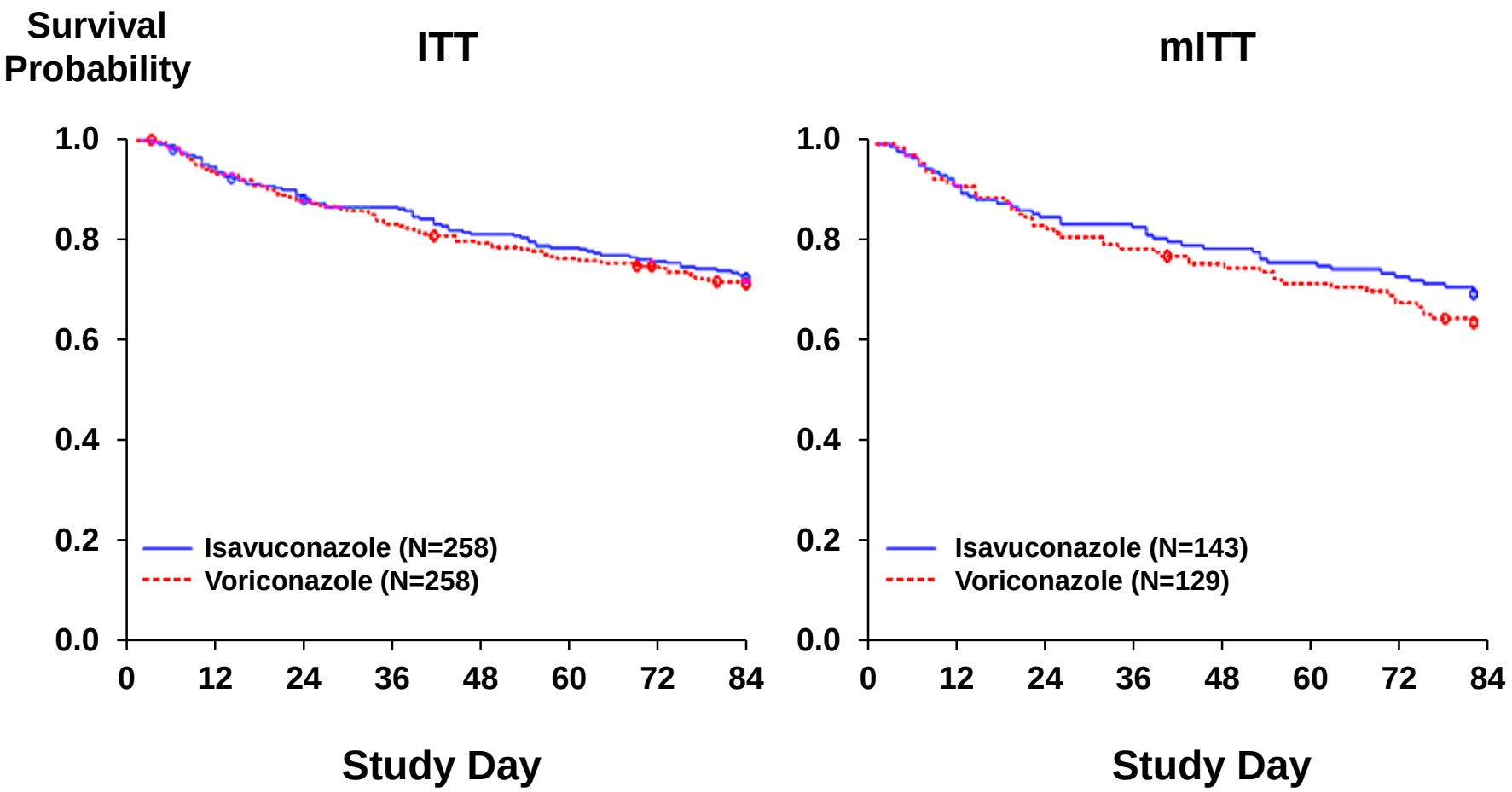
Galactomannan Criteria	
Protocol-Specified	**FDA-Specified**
Serum ≥ 0.5 x 2 values or Serum ≥ 0.7 x 1 value	**Serum ≥ 0.5 x 2 values or Serum or BAL ≥ 1 value**

Study 0104: Consistent Efficacy Across Analysis Populations Including FDA-mITT

	Crude Mortality n/N (%) ISA	VRC
Day 42 ITT	48/258 (18.6)	52/258 (20.2)
Day 42 mITT	28/143 (19.6)	30/129 (23.3)
Day 42 mITT-FDA	28/147 (19.0)	28/128 (21.9)
Day 42 myITT	23/123 (18.7)	24/108 (22.2)
Day 84 ITT	75/258 (29.1)	80/258 (31.0)
Day 84 mITT	43/143 (30.1)	48/129 (37.2)
Day 84 mITT-FDA	41/147 (27.9)	43/128 (33.6)
Day 84 myITT	35/123 (28.5)	39/108 (36.1)

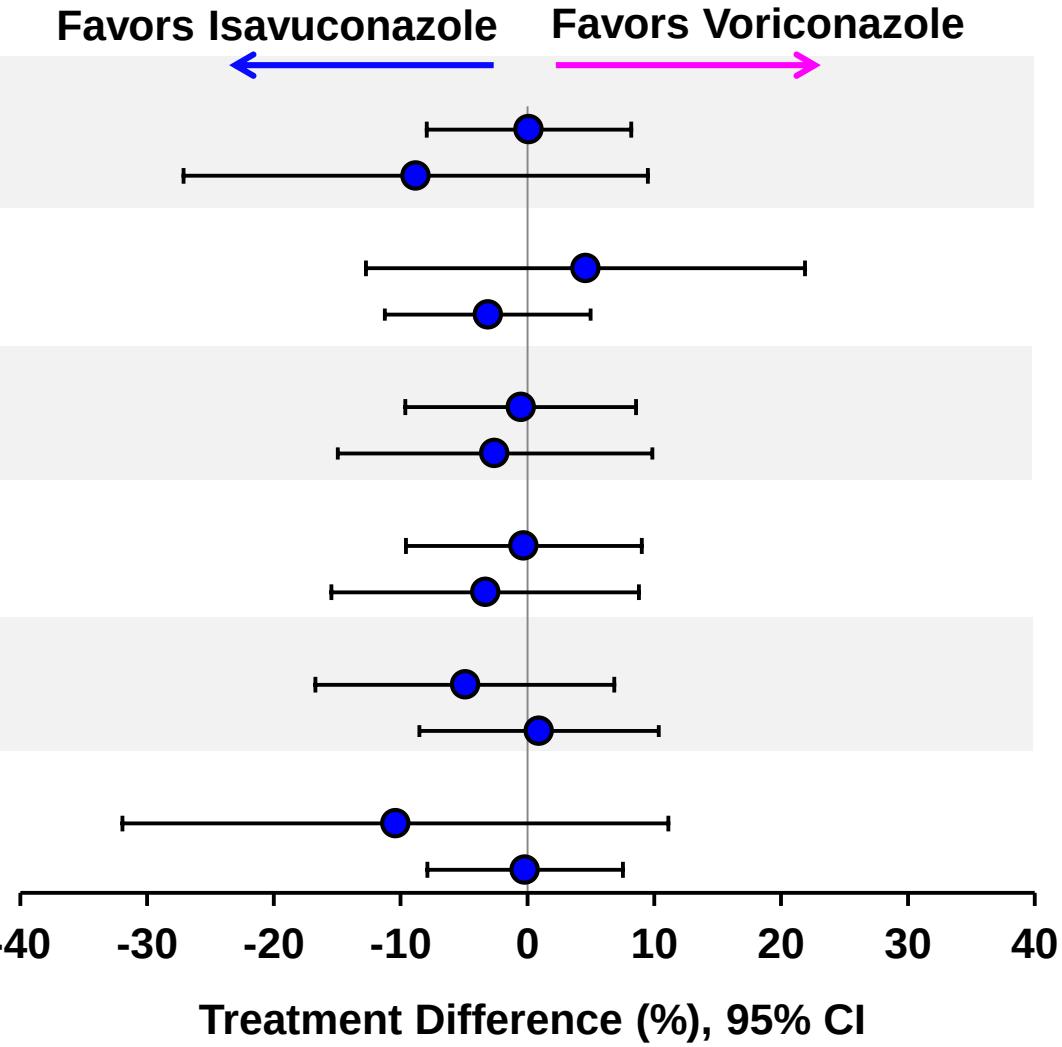


Study 0104: Survival Probabilities Over Time (ITT and mITT)



Study 0104: All-Cause Mortality Through Day 42 by Subgroups (ITT)

Subgroup	ISA N	VRC N
Hematologic Malignancy		
Yes	211	222
No	47	36
Allogeneic HSCT		
Yes	54	51
No	204	207
Active Malignancy		
Yes	173	187
No	85	71
Neutropenia		
Presence	163	175
Absence	95	83
T-Cell Immunosuppressant		
Yes	111	109
No	147	149
Corticosteroids		
Yes	48	39
No	210	219



Study 0104: DRC-Assessed Overall Response Similar Between Treatment Groups

mITT Response at EOT	Isavuconazole N = 143 %	Voriconazole N = 129 %
Success	35.0	36.4
Adjusted Treatment Difference* (95% CI)	1.6 (-9.3, 12.6)	
Complete	11.9	10.1
Partial	23.1	26.4
Failure	65.0	63.6
Stable	29.4	25.6
Progression	35.7	38.0

*Treatment difference (voriconazole – isavuconazole): calculated by a stratified Cochran–Mantel–Haenszel method (strata: allogeneic HSCT, active malignancy status, and geographic region)

Study 0104: Totality of Data Support Invasive Aspergillosis Indication

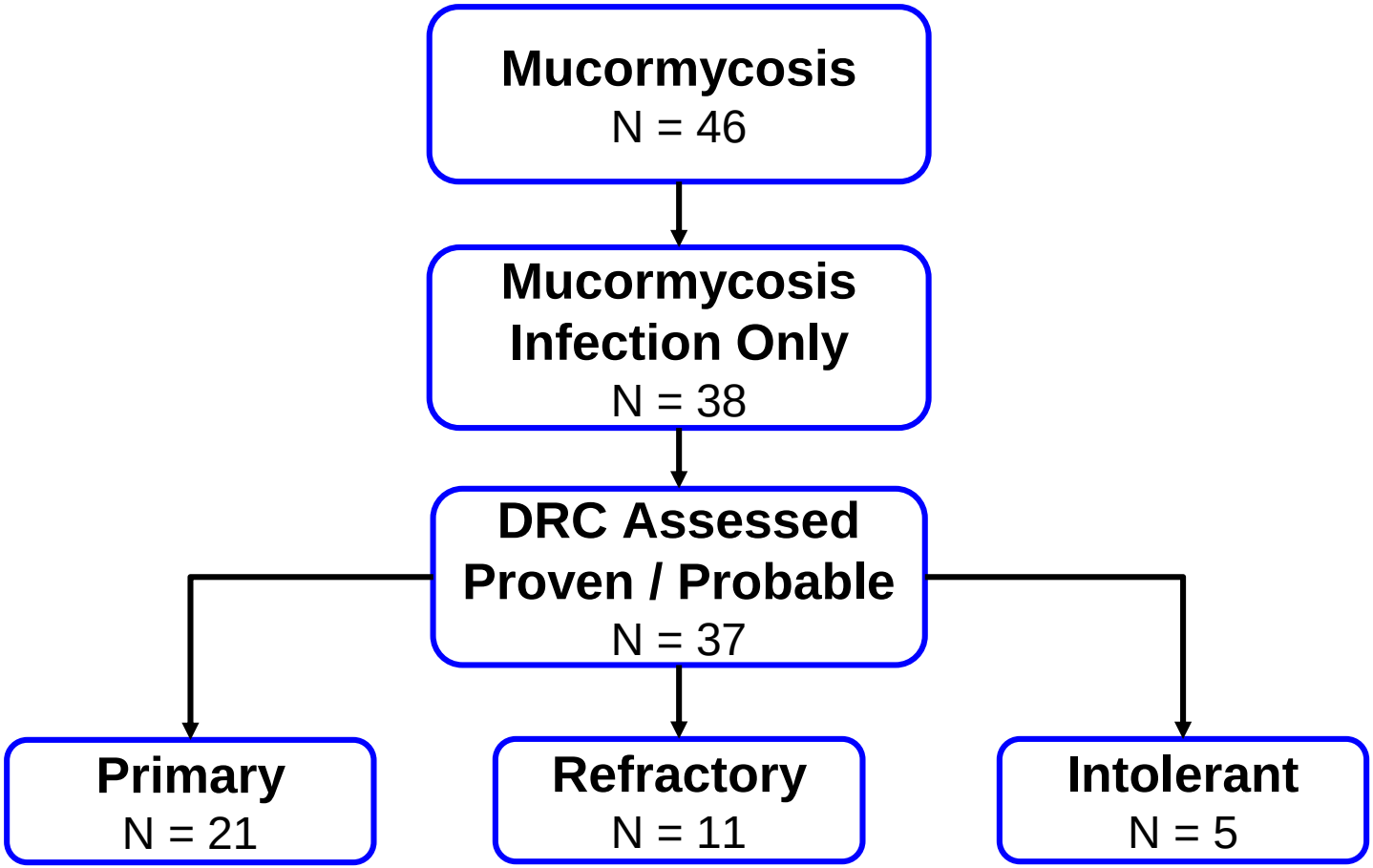
- Large randomized controlled clinical trial
- Primary efficacy objective met
  - Isavuconazole non-inferior to voriconazole for all-cause mortality through Day 42
- Outcomes robust and consistent across populations, subgroups, and time points
- Key secondary endpoint supportive of primary analysis

Study 0103:
Invasive Mucormycosis Indication

Study 0103: Design

- International, open-label, single-arm study
- Adults ≥ 18 years
- Range of rare moulds, yeasts, dimorphic fungi
- Same dosing regimen as in Study 0104
  - Treatment duration up to 180 days
- Primary therapy, refractory, intolerant
- 146 received isavuconazole

Study 0103: Mucormycosis Analysis Populations



Study 0103: Baseline Conditions Mucormycosis

Baseline Risk Factors	Total N = 37 %
Hematologic Malignancy	59.5
Active Malignancy	48.6
T-cell Immunosuppressants	48.6
HSCT	35.1
Neutropenia	27.0
Diabetes	10.8
Solid Organ Transplant	8.1

Study 0103: Treatment Duration Mucormycosis

mITT Population	Total N = 37
Total Duration (days)	
Mean (SD)	133 (193)
Median (Min-Max)	84 (2-882)

Phase 3 Study 0103: Mucormycosis Efficacy Results

Study 0103: DRC-Assessed Overall Response for Mucormycosis

Overall Response at EOT	Primary N = 21 %	Refractory N = 11 %	Intolerant N = 5 %	Total N = 37 %
Success	31.6	36.4	20.0	31.4
Complete	15.8	18.2	0	14.3
Partial	15.8	18.2	20.0	17.1
Failure	68.4	63.6	80.0	68.6
Stable	31.6	18.2	40.0	28.6
Progression	36.8	45.5	40.0	40.0

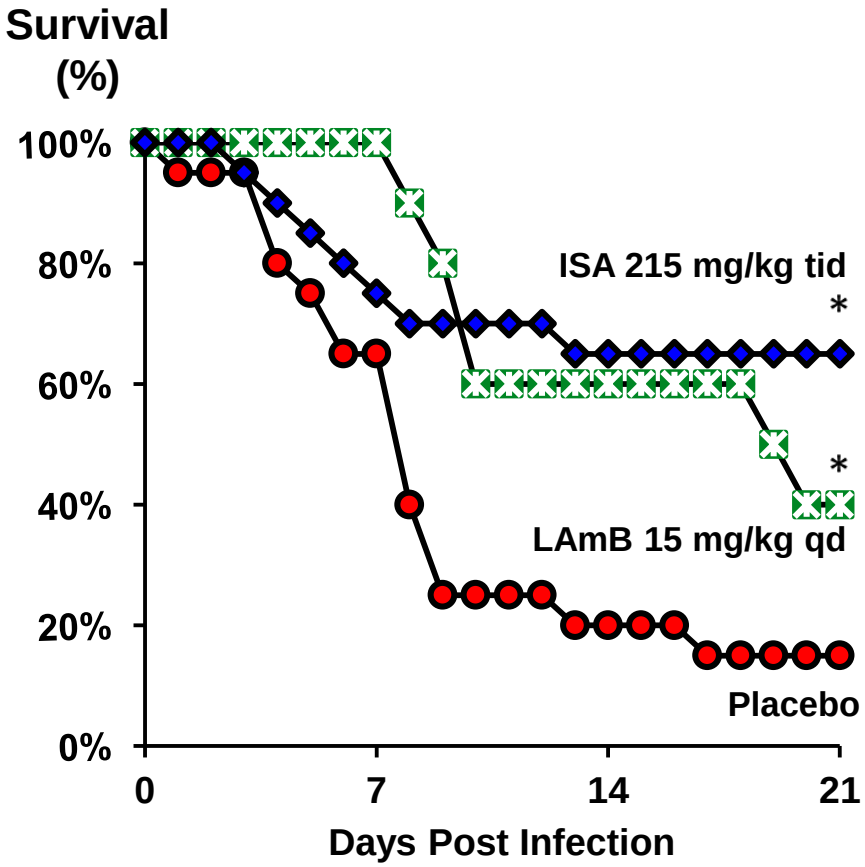
Study 0103: All-Cause Mortality Mucormycosis

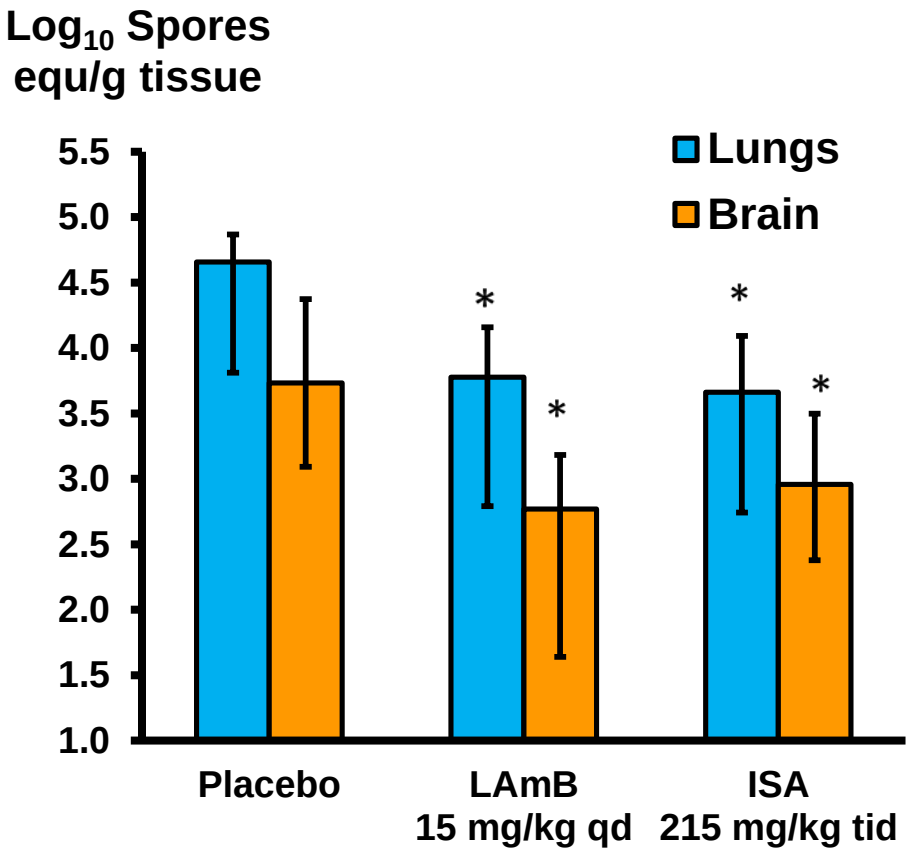
Outcome mITT Mucorales	Primary N = 21 %	Refractory N = 11 %	Intolerant N = 5 %	Total N = 37 %
Day 42	33.3	45.5	40.0	37.8
Day 84	42.9	45.5	40.0	43.2

Study 0103: Invasive Mucormycosis – Support for Data Interpretation

- Within context of large randomized controlled trial (Study 0104) with established efficacy
- Animal models of invasive mucormycosis
- Literature evaluation of natural history
  - Mortality rates in untreated and treated patients
- Matched-case control analysis

Invasive Mucormycosis: Neutropenic Mice-Infected with *Rhizopus oryzae* Increased Survival, Decreased Fungal Burden

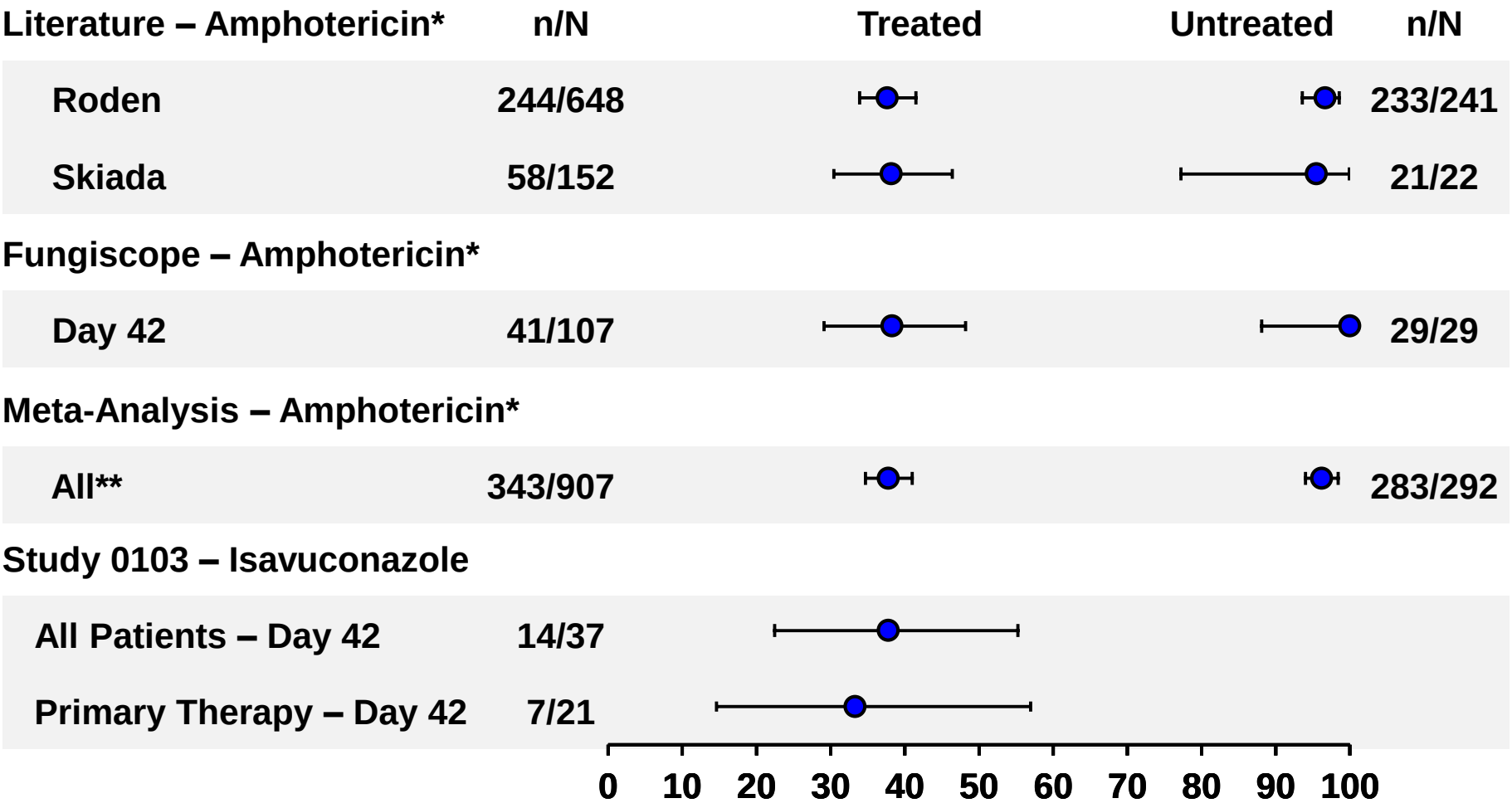




*p = 0.025 or 0.004 for LAmB or ISA compared to placebo mice
N = 20 / group for placebo and ISA mice; N = 10 / group for LAmB mice
Luo et al., 2014.

*p < 0.05 compared to placebo mice
N = 9 mice/group
Luo et al., 2014.

Invasive Mucormycosis: Mortality-Treated and Untreated



*Amphotericin B deoxycholate or lipid formulations
**Roden, Skiada, Fungiscope

Invasive Mucormycosis: Matched Case-Control Methods

- Isavuconazole for primary therapy from Study 0103
- Amphotericin* for primary therapy from Fungiscope
- Matching criteria
  - Severe disease
  - Hematologic malignancy
  - Therapeutic debridement
- Matching conducted independently and blinded to outcomes
  - Up to 3 controls for each 0103 case
- Day 42 mortality rates analyzed

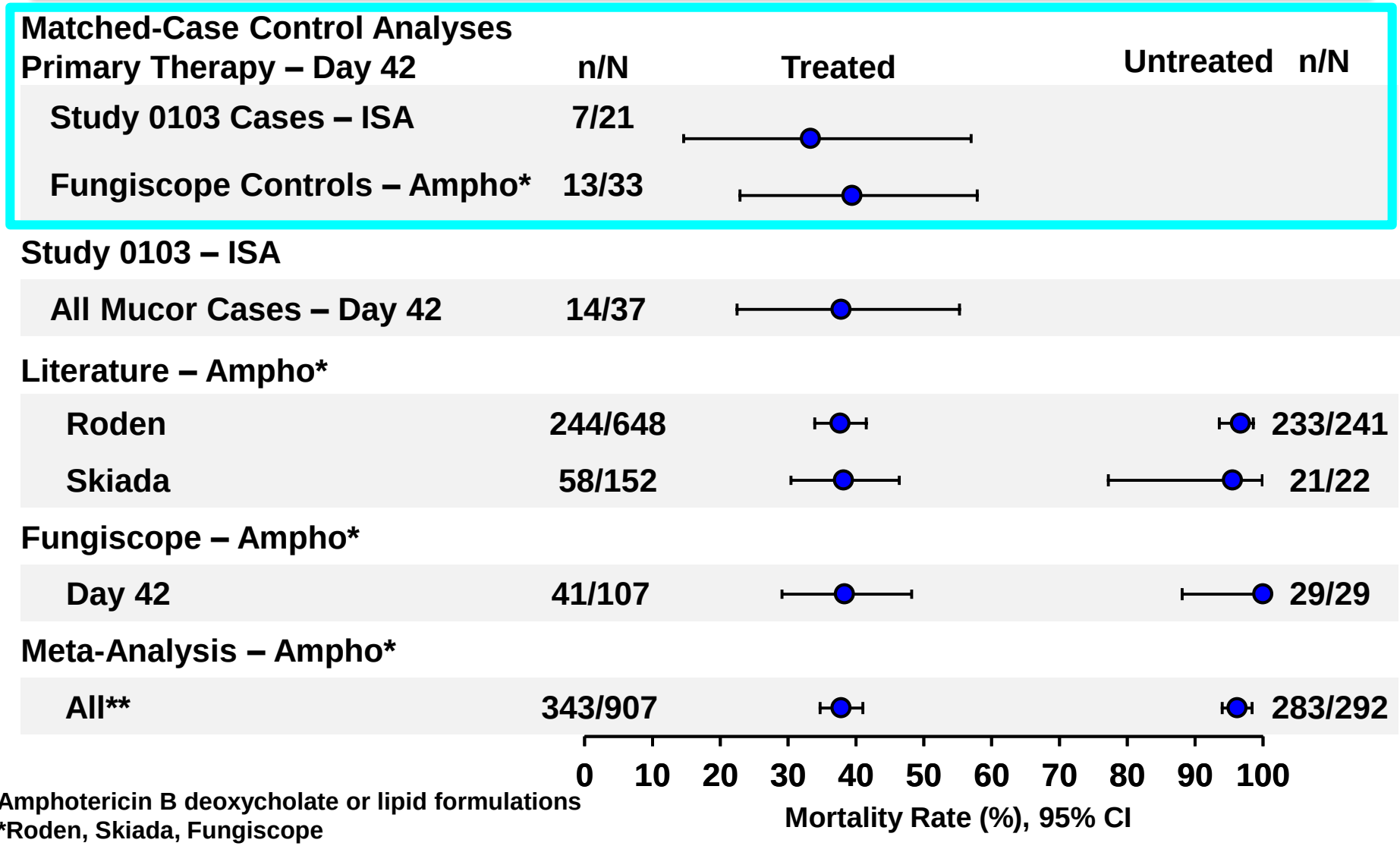
***Amphotericin B deoxycholate or lipid formulations**

Invasive Mucormycosis: Matched Case-Control Disposition

- All 21 primary cases matched to ≥ 1 control
- 33 matched controls identified

Matching Criterion	Study 0103 N = 21 %	Matched Controls N = 33 %
Severe Disease	57.1	39.4
CNS Involvement	28.6	24.2
Disseminated Disease	38.1	24.2
Hematologic Malignancy	52.4	54.5
Therapeutic Debridement	42.9	39.4

Invasive Mucormycosis: Similar Mortality Rate Study 0103 Cases and Matched Controls



*Amphotericin B deoxycholate or lipid formulations
**Roden, Skiada, Fungiscope

Isavuconazole: Totality of Data Support Invasive Mucormycosis Indication

- Animal models
  - Superior survival and reduction in fungal burden relative to placebo
  - Similar outcomes to liposomal amphotericin
- Clinical efficacy
  - Better relative to untreated literature controls
  - Similar relative to amphotericin* from literature and matched controls

*Amphotericin B deoxycholate or lipid formulations

Efficacy Demonstrated for Invasive Aspergillosis and Mucormycosis

- Invasive Aspergillosis
  - Primary efficacy objective met
  - Isavuconazole non-inferior to voriconazole for all-cause mortality through Day 42
  - Consistent outcomes across populations, subgroups, and time points
- Invasive Mucormycosis
  - Totality of preclinical and clinical data support efficacy

Safety of Isavuconazole

Salim Mujais, MD

Vice President

Global Medical Head Infectious Disease / Immunology / Transplant

Astellas Pharma

Presentation Outline

- Safety population
- Study drug exposure
- Detailed comparative safety – Study 0104
  - Overall safety
  - Specific safety aspects
- Effects on cardiac repolarization
- Subgroup analysis
- Safety in other studies – Study 0103

Global Safety Population – Phase 1

	Studies N	Subjects N	Received Isavuconazole N
Total	**44**	**2,166**	**1,692**
Phase 1 Studies	**40**	**1,322**	**1,145**
Phase 2 Studies	**2**	**182**	**144**
Phase 3 Studies	**2**	**662**	**403**

- 8 PK studies in volunteers and special populations
- 5 bioavailability, food effect and mass balance studies
- 2 pharmacodynamic studies (tQT)
- 25 drug-drug interaction studies

Global Safety Population – Phase 2

	Studies N	Subjects N	Received Isavuconazole N
Total	**44**	**2,166**	**1,692**
Phase 1 Studies	**40**	**1,322**	**1,145**
Phase 2 Studies	**2**	**182**	**144**
Phase 3 Studies	**2**	**662**	**403**

- Treatment of esophageal candidiasis
- Fungal prophylaxis in acute myeloid leukemia

Global Safety Population – Phase 3

	Studies N	Subjects N	Received Isavuconazole N
Total	**44**	**2,166**	**1,692**
Phase 1 Studies	**40**	**1,322**	**1,145**
Phase 2 Studies	**2**	**182**	**144**
Phase 3 Studies	**2**	**662**	**403**

- Study 0104 invasive aspergillosis
- Study 0103 mucormycosis and rare moulds

Studies 0104 and 0103: Drug Exposure in Phase 3 Studies

	Isavuconazole 0104 N = 257	Isavuconazole 0103 N = 146
Total Duration (days)		
Mean (SD)	47 (32.3)	127 (130.5)
Median	45	94
Cumulative Duration, %		
≥ 14 Days	74.3	87.0
≥ 28 Days	61.9	75.3
≥ 42 Days	53.7	70.5
≥ 84 Days	23.3	57.5
≥ 126 Days	--	45.9
≥ 180 Days	--	35.6

Study 0104: Safety Population

- Safety overview
  - Target patient population
  - Double-blind and randomized
  - Active comparator – voriconazole
  - Subgroup analysis

Study 0104: High Morbidity Target Patient Population – Safety Population

Parameter	Isavuconazole N = 257 %	Voriconazole N = 259 %
Hematologic Malignancy	82.1	85.7
Active Malignancy	67.3	72.2
Neutropenia	63.4	67.6
T-cell Immunosuppressant	43.2	42.1
HSCT	21.0	19.7
Use of Corticosteroids	18.7	15.1

Study 0104: Overview of Safety

	Isavuconazole N = 257 %	Voriconazole N = 259 %
AEs Leading to Death	24.1	27.8
SAE	52.1	57.5
AEs	96.1	98.5
Study Drug-related AEs	42.4	59.8
AEs Leading to Permanent Discontinuation of Study Drug	14.4	22.8

Study 0104: AEs Leading to Death (SOC ≥ 1%)

System Organ Class	Isavuconazole N = 257 %	Voriconazole N = 259 %
Overall	24.1	27.8
Infections and Infestations	10.9	6.9
Respiratory, Thoracic and Mediastinal Disorders	5.4	4.6
Neoplasms Benign, Malignant and Unspecified	3.9	8.1
Cardiac Disorders	1.6	1.9
Nervous System Disorders	1.2	2.7
General Disorders	0.8	3.1

Study 0104: Most Common SAEs (SOC ≥ 5%)

System Organ Class	Isavuconazole N = 257 %	Voriconazole N = 259 %
Overall	52.1	57.5
Infections and Infestations	19.8	23.6
Respiratory, Thoracic and Mediastinal Disorders	16.0	16.6
Blood and Lymphatic System Disorders	10.9	6.6
Neoplasms Benign, Malignant and Unspecified	7.0	11.2
Nervous System Disorders	6.6	6.2
General Disorders and Administration Site Conditions	4.3	7.3

Study 0104: Most Common AEs

Preferred Term	Isavuconazole N = 257 %	Voriconazole N = 259 %
AEs	96.1	98.5
Nausea	27.6	30.1
Vomiting	24.9	28.2
Diarrhea	23.7	23.2
Pyrexia	22.2	30.1
Hypokalaemia	17.5	21.6
Headache	16.0	14.7
Constipation	14.0	20.8
Dyspnea	13.2	11.2
Cough	12.8	13.5
Febrile Neutropenia	12.5	14.7

Study 0104: AEs by System Organ Class (SOC) (≥ 5%)

System Organ Class, %	Isavuconazole N = 257	Voriconazole N = 259
Gastrointestinal Disorders	67.7	69.5
Infections and Infestations	59.1	61.0
General Disorders and Admin. Site Conditions	57.6	55.6
Respiratory, Thoracic and Mediastinal Disorders	55.6	56.8
Metabolism and Nutrition Disorders	42.0	46.7
Nervous System Disorders	37.0	34.4
Skin and Subcutaneous Tissue Disorders	33.5	42.5
Investigations	33.1	37.1
Blood and Lymphatic System Disorders	30.0	31.7
Psychiatric Disorders	27.2	33.2
Musculoskeletal and Connective Tissue Disorders	26.8	29.7
Vascular Disorders	26.1	29.7
Renal and Urinary Disorders	21.4	22.4
Cardiac Disorders	16.7	22.0
Eye Disorders	15.2	26.6
Injury, Poisoning and Procedural Complications	12.8	15.1
Hepatobiliary Disorders	8.9	16.2
Immune System Disorders	7.8	9.7
Neoplasms Benign, Malignant and Unspecified	7.4	12.0
Ear and Labyrinth Disorders	5.4	5.0

Study 0104: Differences in AEs – Skin Disorders

- **Skin disorders**
- Eye disorders
- Hepatobiliary disorders

System Organ Class Preferred Term	Isavuconazole N = 257 %	Voriconazole N = 259 %
Skin and Subcutaneous Tissue Disorders	33.5	42.5
Rash	6.6	10.8
Erythema	3.5	5.8
Drug Eruption	1.2	4.2

Study 0104: Differences in AEs – Eye Disorders

- Skin disorders
- **Eye disorders**
- Hepatobiliary disorders

System Organ Class Preferred Term	Isavuconazole N = 257 %	Voriconazole N = 259 %
Eye Disorders	15.2	26.6
Visual Impairment	1.6	7.3
Photophobia	0.8	2.3
Visual Acuity Reduced	0.4	2.3

Study 0104: Differences in AEs – Hepatobiliary Disorders

- Skin disorders
- Eye disorders
- **Hepatobiliary disorders**

System Organ Class Preferred Term	Isavuconazole N = 257 %	Voriconazole N = 259 %
Hepatobiliary Disorders	8.9	16.2
Hyperbilirubinemia	1.9	3.9
Hepatic Function Abnormal	1.6	3.5
Jaundice	0.4	2.3

Study 0104: Liver Enzymes

Parameter	Criteria	Isavuconazole N = 257 %	Voriconazole N = 259 %
ALT	> 3 x ULN	12.4	13.7
	> 5 x ULN	6.8	7.1
	> 10 x ULN	2.0	4.7
AST	> 3 x ULN	9.6	15.3
	> 5 x ULN	5.2	7.5
	> 10 x ULN	1.6	3.1
ALT or AST	> 3 x ULN	15.6	18.8
	> 5 x ULN	8.4	10.6
	> 10 x ULN	2.4	5.5
Alk. Phos.	> 3 x ULN	9.6	13.4

Study 0104: Concurrent Liver Tests Abnormalities

Criteria	Isavuconazole N = 257		Voriconazole N = 259	
	n/N	%	n/N	%
(ALT or AST) > 3 x ULN, Total Bilirubin > 2 x ULN and Alk. Phos. < 2 x ULN	3/251	1.2	7/255	2.7

Changes in Cardiac Repolarization: QT Findings

Thorough QT Study: Effect of Isavuconazole on QT Interval

- Azole antifungals
  - Associated with QT prolongation
- Isavuconazole caused dose-dependent QTc shortening
  - 13 msec at C_{max} of proposed maintenance dose of 200 mg QD
  - Possible mechanism identified, *in vitro* ion channel effects study

Clinical Significance of Observed Electrocardiographic Effect

- Congenital short QT syndrome
  - Extremely rare
  - Associated with serious ventricular arrhythmias
- Drug-induced QT shortening
  - Clinical relevance not established

tQT Study: Outlier Analysis of Extreme QTcF Values

QTcF Category	tQT study 200 mg N = 37	tQT study 600 mg N = 32
≥ 1 ECG Post-baseline, n	37	32
Prolongation Thresholds		
> 480 msec, %	0	0
> 500 msec, %	0	0
Shortening Thresholds		
< 330 msec, %	0	0
< 300 msec, %	0	0

Study 0104: Outlier Analysis of Extreme Post-Baseline QTcF Values

QTcF Category	Isavuconazole N = 257	Voriconazole N = 259
≥ 1 ECG Post-baseline, n	250	252
Prolongation Thresholds		
> 480 msec, %	1.2	4.8
> 500 msec, %	0.4	1.2
Shortening Thresholds		
< 330 msec, %	2.0	2.0
< 300 msec, %	0.4	0

Study 0104: Arrhythmia-Type AEs – SMQ Torsade de Pointes

SMQ Preferred Term	Isavuconazole N = 257 %	Voriconazole N = 259 %
≥ 1 AE in Torsade de Pointes SMQ	5.8	7.3
Syncope	2.7	0.8
Loss of Consciousness	1.2	0
Electrocardiogram QT Prolonged	0.8	3.1
Cardio-respiratory Arrest	0.8	0.8
Cardiac Arrest	0.4	2.3
Ventricular Tachycardia	0	0.8
Sudden Cardiac Death	0	0.4
Torsade de Pointes	0	0

Study 0104: Isavuconazole QT Shortening Conclusion

- Shortening of cardiac repolarization observed in thorough QT studies
- Changes in QTc in clinical studies more variable
- No apparent clinical correlate to ECG finding
  - Analysis of AEs potentially associated with changes in cardiac repolarization

Consistent Safety Profile Across Subgroups

- Treatment differences observed for overall AEs consistent across subgroup analyses
  - Age
  - Gender
  - HSCT status
  - Hematologic malignancy
  - Active malignancy status
  - Baseline neutropenic status

Consistent Safety Profile Across Studies

- Safety findings in Study 0104 concordant with
  - Other studies in clinical development program
  - Safety findings in patients with invasive mucormycosis

Studies 0104 and 0103: Overview of Safety

	Isavuconazole Study 0104 N = 257 %	Isavuconazole Study 0103 N = 146 %
AEs Leading to Death	24.1	30.1
SAE	52.1	61.0
AEs	96.1	95.2
Study Drug-related AEs	42.4	41.1
AEs Leading to Permanent Discontinuation of Study Drug	14.4	13.0

Isavuconazole Risk Management: Azole Class-Specific Risks

Azole Class Risks	ISA Identified	ISA Potential	Risk Management
Hepatotoxicity	X		Labeling Routine Pharmacovigilance
Infusion-Related Reactions	X		
Severe Cutaneous Reactions		X	
Embryo-fetal Toxicity		X	
Effect on Children Exposed (Breast Milk)		X	
Development of Resistance		X	Post-marketing Surveillance

Isavuconazole Risk Management: Isavuconazole-Specific Risk

Safety Concern	Proposed Labeling
Arrhythmia Due to QT Shortening	**Contraindications –** Patients with Familial Short QT syndrome

- Proposed labeling similar to rufinamide (Banzel®) with known QT shortening

Well-Characterized Safety Profile

- Isavuconazole safety profile broadly similar to voriconazole except
  - Fewer drug-related AEs
  - Fewer AEs
    - Skin disorders
    - Eye disorders
    - Hepatobiliary disorders
  - Shortened QTc interval
- Safety profile of isavuconazole similar across target indications

Benefit-Risk

Bernhardt Zeiher, MD, FACP, FCCP
Executive Vice President
Global Development
Astellas Pharma

Alternative Therapies Needed for Invasive Aspergillosis and Mucormycosis

- Invasive aspergillosis
  - Voriconazole first-line therapy[1]
    - Limitations include PK characteristics and safety profile
- Invasive mucormycosis
  - Amphotericin B first-line therapy[2]
    - Limitations include only IV formulation and renal toxicity

1. Walsh et al., 2008. 2. Cornely et al., 2014.

Isavuconazole Clinical Pharmacologic Profile

- Predictable PK
- Long half-life, Once-daily dosing
- No cyclodextrin in IV formulation
- Manageable DDI profile

Isavuconazole Demonstrated Efficacy in Both Indications

Predictable PK	Non-inferior all-cause mortality through Day 42
Long half-life, Once-daily dosing	Comparable overall success rate at EOT
No cyclodextrin in IV formulation	Consistent efficacy across populations, subgroups and time
Manageable DDI profile	Active in mucormycosis

Isavuconazole Safety Profile

Predictable PK	Non-inferior all-cause mortality through day 42	Similar safety profile to other azoles
Long half-life, once-daily dosing	Comparable overall success rate at EOT	QTc shortening
No cyclodextrin in IV formulation	Consistent efficacy across populations, subgroups and time	Lower incidence of drug-related AEs
Manageable DDI profile	Active in mucormycosis	No signal of nephrotoxic effects

Favorable Benefit-Risk Profile for Isavuconazole

Predictable PK	Non-inferior all-cause mortality through day 42	Similar safety profile to other azoles
Long half-life, once-daily dosing	Comparable overall success rate at EOT	QTc shortening
No cyclodextrin in IV formulation	Consistent efficacy across populations, subgroups and time	Lower incidence of drug-related AEs
Manageable DDI profile	Active in mucormycosis	No signal of nephrotoxic effects

Astellas Pharma
Isavuconazole

Food and Drug Administration

Anti-infective Drug Advisory Committee

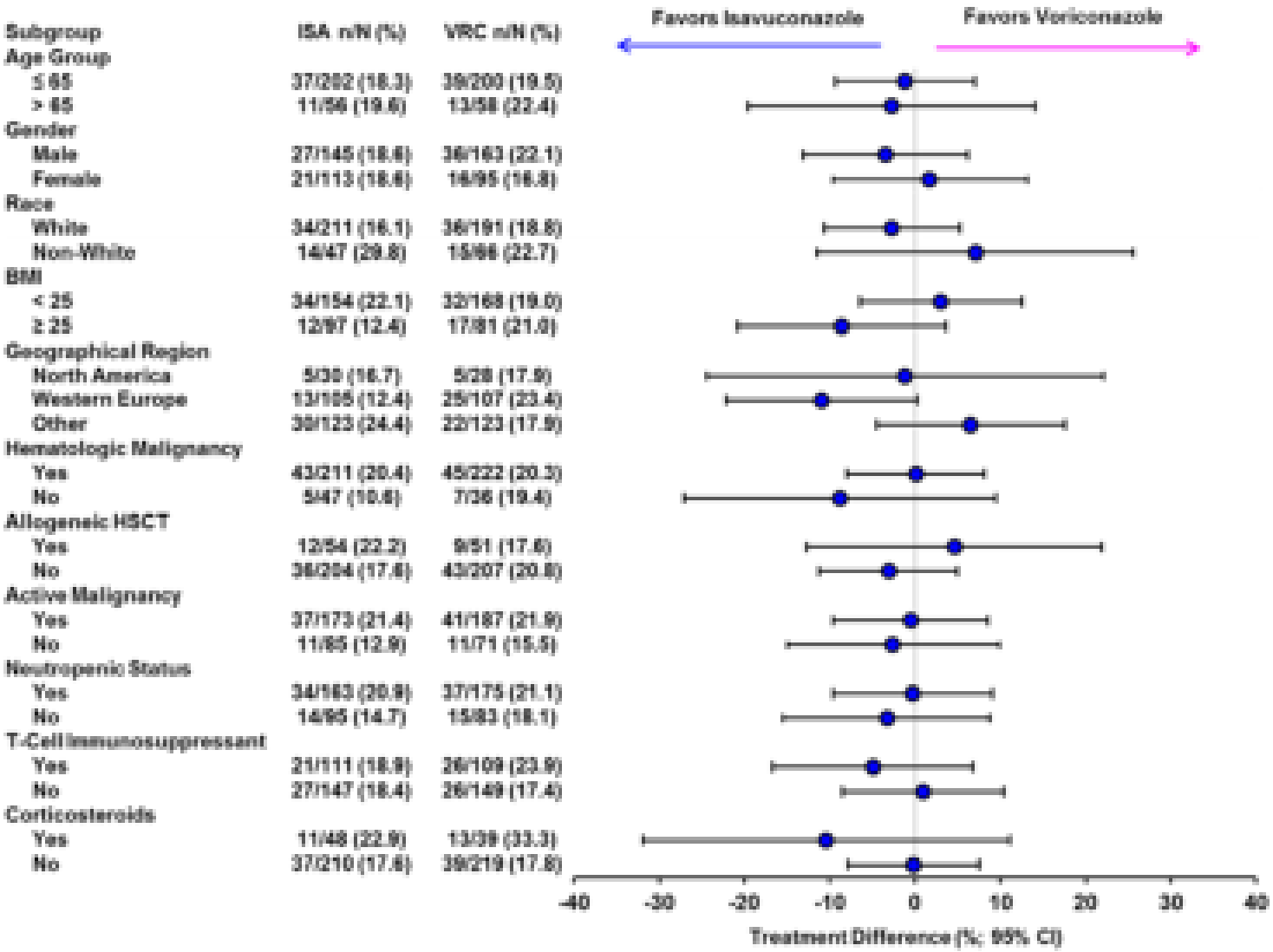
January 22, 2015

PK Differences Between Healthy Western and Chinese Subjects

	Dose Normalized AUC (h·μg/mL)	
	Western Subjects N = 116	Chinese Subjects N = 37
Mean	85.5	130
SD	27.1	42.9
Median	80.1	117
Min - Max	32.9 - 174	69.0 - 267

- Exposure in Chinese subjects Is approximately 1.5 times that found in Western subjects

Figure 18: All-cause Mortality Through Day 42 - Number of Patients and Treatment Differences with 95% CIs by Subgroup (ITT Population; 0104)



Study 0104: All-Cause Mortality Day 42
Top 10 Enrolling Countries

Region / Country	Number Patients Dosed	Isavuconazole		Voriconazole	
		n/N	%	n/N	%
W. Eu / Belgium	116	6/61	9.8	14/55	25.5
Other / Israel	59	6/33	18.2	2/26	7.7
N. A. / United States	54	5/29	17.2	4/25	16.0
W. Eu / Germany	51	4/22	18.2	8/29	27.6
Other / Thailand	31	2/12	16.7	4/19	21.1
Other / India	29	5/12	41.7	5/17	29.4
W. Eu / France	27	3/14	21.4	2/13	15.4
Other / China	26	1/10	10.0	4/16	25.0
Other / Russia	21	2/14	14.3	1/7	14.3
Other / S. Korea	20	5/8	62.5	1/12	8.3

Table 13: Sensitivity Analyses for All-cause Mortality through Day 42 (ITT Population; 0104)

Analysis Method Outcomes, n (%)	Isavuconazole (n = 258)	Voriconazole (n = 258)
Minimum Risk		
All-cause mortality†	48 (18.6)	52 (20.2)
Adjusted treatment difference (95% CI)‡	-1.1 (-7.842, 5.624)	
Without Adjustment for Stratification Factors		
All-cause mortality†	48 (18.6)	52 (20.2)
Crude treatment difference (95% CI)§	-1.6 (-8.771, 5.670)	

† 5 patients (3 isavuconazole and 2 voriconazole) with unknown survival status were counted as deaths.

‡ Adjusted treatment difference (isavuconazole−voriconazole) and 95% CIs are calculated by a stratified Minimum Risk method with stratification factors: Geographical Regions, Allogeneic HSCT Status and Active Malignancy Status.

§ Crude treatment difference is calculated by subtracting voriconazole from isavuconazole (isavuconazole−voriconazole) without stratification factors and the 95% CI is calculated based on a normal approximation.

Study 0104: All-Cause Mortality Through Day 42 and Day 84: Worst-Case Analysis (ITT)

Timepoint	Outcome	Isavuconazole N = 258		Voriconazole N = 258		Adjusted Difference, (95% CI)
		n	%	n	%	
Day 42	All-Cause Mortality	48	18.6	50	19.4	-0.3 (-6.9, 6.4)
	Known Deaths	45	17.4	50	19.4	
	Unknown Survival Status	3	1.2	-*	-	
Day 84	All-Cause Mortality	75	29.1	75	29.1	0.7 (-6.9, 8.3)
	Known Deaths	72	27.9	75	29.1	
	Unknown Survival Status	3	1.2	-**	-	

*2 Unknown survival status patients assumed alive for this analysis
**5 Unknown survival status patients assumed alive for this analysis

Table 32: Case Control Matching

Study 0103 Cases (n = 21), n (%) of patients	Number of Matched Controls
5 (23.8)	3
2 (9.5)	2
14 (66.7)	1

Case Matched Control: Association Between Mortality and Baseline Characteristics

- Baseline characteristics were identified (p-value≤0.2 from a chi-square test) from a logistic regression (forward selection procedure):
  - Disseminated Disease, Surgery, Hematologic Malignancy, and CNS Involvement.
- Model's goodness-of-fit was evaluated by Hosmer-Lemeshow test
  - (p-value=0.38)
- Mean predicted mortalities from cases (study 0103) and Fungiscope controls were calculated from 10,000 bootstrap simulations

	All-Cause Mortality	95% CI
Observed Mortality - Study 0103 Primary Therapy Cases	33.3% (7/21)	(14.6%, 57.0%)
Observed Mortality - Fungiscope Matched-Controls	39.4% (13/33)	(22.9%, 57.9%)
Predicted Mortality for Study 0103 Primary Therapy Cases	47.0%	(33.3%, 61.1%)
Predicted Mortality for Fungiscope Matched-Controls	39.4%	(29.8%, 49.2%)

Study 0104: Severe Cutaneous Adverse Reactions

	Isavuconazole N = 257 n (%)	Voriconazole N = 259 n (%)
Dermatitis exfoliative	1 (0.4%)	1 (0.4%)
Erythema multiforme	2 (0.8%)	0
Shock	0	1 (0.4%)
Toxic skin eruption	0	1 (0.4%)

Study 0104: All-Cause Mortality at Day 42 by Neutropenic Status

		Isavuconazole		Voriconazole	
ACM Day 42	Neutropenia Status	n/N	%	n/N	%
mITT	Remained	20/65	30.8	16/55	29.1
	Resolved	2/23	8.7	1/18	5.6
ITT	Remained	31/115	27.0	33/127	26.0
	Resolved	3/48	6.3	4/48	8.3

Table 14: All-cause Mortality through Day 42 by IFD Category (ITT Population)

IFD Category, n/n (%)	Isavuconazole (n = 258)	Voriconazole (n = 258)
Proven	7/29 (24.1)	7/36 (19.4)
Probable	21/114 (18.4)	23/93 (24.7)
Possible	15/88 (17.0)	19/108 (17.6)
No IFD	5/27 (18.5)	3/21 (14.3)

Table 78: All-cause Crude Mortality through Day 42 and Day 84 (All Other mITT Populations; 0103)

Time Point Outcome	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infection (n = 15)
Through Day 42					
All-cause Mortality†	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	3 (20.0%)
Deaths	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	2 (13.3%)
Unknown Survival Status	0	0	0	0	1 (6.7%)
Through Day 84					
All-cause Mortality†	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	5 (33.3%)
Deaths	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	4 (26.7%)
Unknown Survival Status	0	0	0	0	1 (6.7%)

† A patient with a last known survival status before day 42 or before day 84 or missing, with the last assessment day before day 42 or before day 84, was counted as a death.

Table 25: Primary Reason for Treatment Discontinuation (mITT-Mucorales Population; 0103)

n (%) of patients	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation	13 (61.9)	9 (81.8)	2 (40.0)	24 (64.9)
Primary reason for treatment discontinuation				
Death	6 (28.6)	3 (27.3)	2 (40.0)	11 (29.7)
Adverse event/intercurrent illness	2 (9.5)	4 (36.4)	0	6 (16.2)
Did not cooperate	3 (14.3)	1 (9.1)	0	4 (10.8)
Insufficient therapeutic response	1 (4.8)	1 (9.1)	0	2 (5.4)
Admin/other	1 (4.8)	0	0	1 (2.7)

Table 26: Summary of Demographics and Baseline Characteristics by Therapy Status (mITT-Mucorales Population; 0103) (1 of 2)

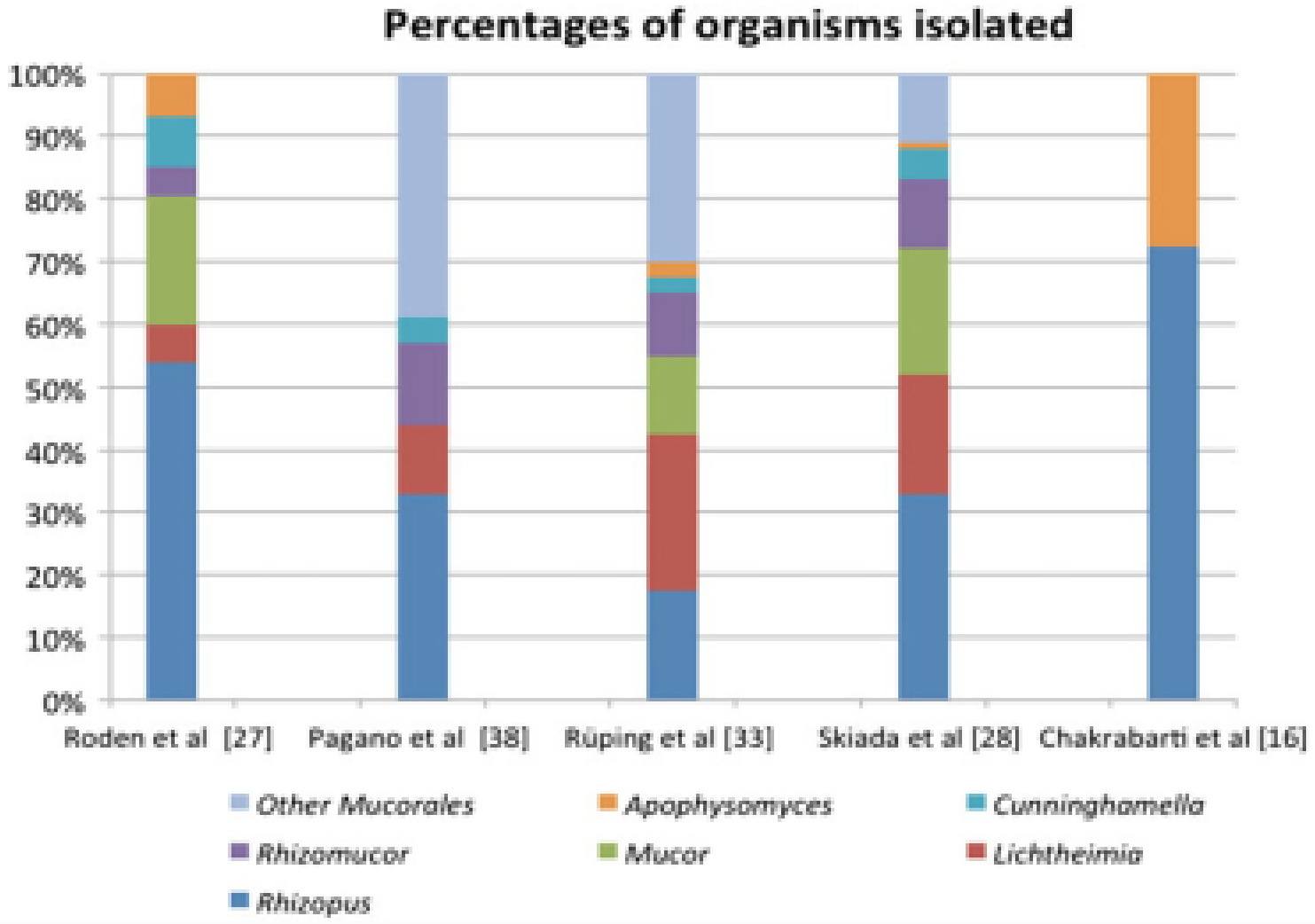
Parameter Category/Statistic	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Age, Mean (SD), years	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)
Sex, Male, n (%)	17 (81.0)	8 (72.7)	5 (100.0)	30 (81.1)
Race, n (%)				
White	12 (57.1)	10 (90.9)	3 (60.0)	25 (67.6)
Black or African American	1 (4.8)	1 (9.1)	2 (40.0)	4 (10.8)
Asian	8 (38.1)	0	0	8 (21.6)
Ethnicity, n (%)				
Hispanic or Latino	1 (4.8)	0	0	1 (2.7)
Not Hispanic or Latino	20 (95.2)	11 (100.0)	5 (100.0)	36 (97.3)
Geographic Region, n (%)				
North America	7 (33.3%)	4 (36.4%)	5 (100.0%)	16 (43.2%)
Western Europe	1 (4.8%)	4 (36.4%)	0	5 (13.5%)
Other Regions†	13 (61.9%)	3 (27.3%)	0	16 (43.2%)

† Other Regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon and Israel.

Study 0103: Mucorales Primary Therapy- Primary Reasons for Treatment Discontinuations

Reason for Discontinuation	Days on Therapy	Day of Death	DRC-Outcome at EOT DRC-Attributed Mortality Additional Comments
AE Intercurrent Illness	509	517	DRC-assessed as complete response At death DRC-assessed no evidence of IFD Died: malignant neoplasm progression
AE Intercurrent Illness	33	56	DRC-assess as stable failure At death DRC-assessed no evidence of IFD Died: renal failure acute
Did Not Cooperate (Withdrew Consent)	106	-	DRC-assessed as stable failure Last known alive day 107
Did Not Cooperate (Withdrew Consent)	4	5	DRC-assessed as progression At death DRC-assessed as due to IFD Died: cerebral infarction
Did Not Cooperate (Withdrew Consent)	15	17	DRC-assessed as progression At death DRC-assessed as due to IFD Died: cardio-respiratory arrest
Insufficient Therapeutic Response	102	-	DRC-assessed as stable Last known alive day 328
Admin. / Other (General Condition of Pt.)	2	3	DRC-assessed as progression At death DRC-assessed as due to IFD Died: mucormycosis

Frequency of Mucorales Organisms



Petrikkos et al Clin Infect Dis 2012;54(Suppl 1):S23-34

Treatment of Mice with Mucormycosis Median Survival Time (Days)

Mucorales	Clinical Frequency	Placebo	AmB-based	POS	ISA
Rhizopus	50-70%*	4-8‡	15-19‡	4-13‡	>21‡
Mucor	10-20%*	4-7‡	7->30‡	6-11‡	ND
Lichtheimia	5-25%*	3-4‡	>14‡	3-11‡	>7‡
Apophysomyces	5-28%*	4-7‡	5-30‡	7-30‡	ND

* Roden et al 2005; Chakrabarti et al 2009

‡ Sun et al 2003; Dannaoui et al 2003; Luo et al 2013; Salas et al. 2012 AAC; Salas et al 2012 JAC; Warn & Sharp ECCMID 2014